



US009273024B2

(12) **United States Patent
North**(10) **Patent No.: US 9,273,024 B2**
(45) **Date of Patent: Mar. 1, 2016**(54) **SYNTHESIS OF CYCLIC CARBONATES**(71) Applicant: **UNIVERSITY OF NEW CASTLE
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patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.(21) Appl. No.: **13/887,787**(22) Filed: **May 6, 2013**(65) **Prior Publication Data**

US 2013/0317237 A1 Nov. 28, 2013

Related U.S. Application Data(63) Continuation of application No. 12/921,264, filed as
application No. PCT/GB2009/000624 on Mar. 6,
2009, now abandoned.(30) **Foreign Application Priority Data**Mar. 7, 2008 (GB) 0804345.7
Nov. 18, 2008 (GB) 0821092.4(51) **Int. Cl.****C07D 317/38** (2006.01)**C07F 5/06** (2006.01)**C07D 317/34** (2006.01)**C07D 317/36** (2006.01)(52) **U.S. Cl.**CPC **C07D 317/38** (2013.01); **C07D 317/34**
(2013.01); **C07D 317/36** (2013.01); **C07F**
5/069 (2013.01); **C07B 2200/11** (2013.01)(58) **Field of Classification Search**CPC **C07D 317/38**
See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**2,773,070 A * 12/1956 Lichtenwalter et al. 549/230
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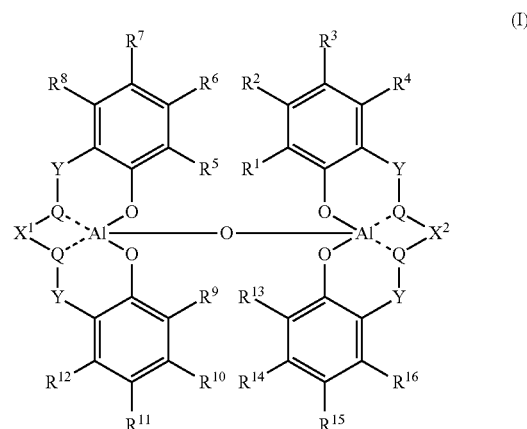
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(57)

ABSTRACT

A dimeric aluminum(salen) catalyst of formula I:

wherein: (a) at least one R group is selected from L-A, and/or
(b) at least one of X group is a divalent C3-7 heterocyclene
group, containing a ring atom which is a quaternary nitrogen
atom paired with a counterion selected from Cl, Br and I;
and/or (c) at least one X group is a C2-5 alkylene chain or a
C1-3 bisoxyalkylene chain, substituted by a group -Q-L-A;
and/or(ii) (a) one R group is L-A', or (b) one X group is a divalent
C3-7 heterocyclene group, containing a ring atom which is a
quaternary nitrogen forming part of an ammonium linking
group bound to a solid support and paired with a counterion
selected from Cl, Br and I; or (c) one X group is a C2-5
alkylene chain or a C1-3 bisoxyalkylene chain, substituted by
a group -Q-L-A'.**15 Claims, 1 Drawing Sheet**

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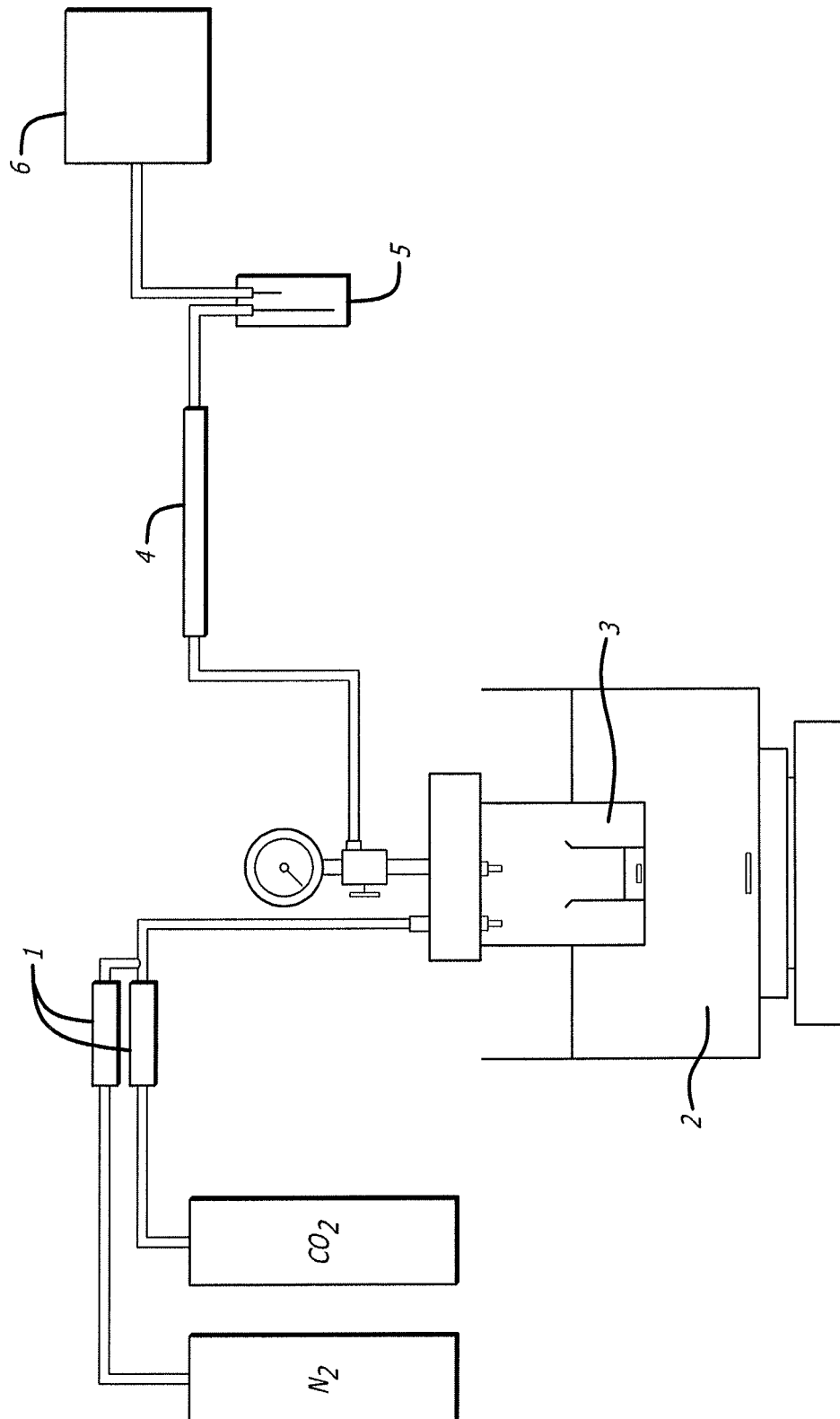
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SYNTHESIS OF CYCLIC CARBONATES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 12/921,264, Filed Sep. 7, 2010, which claims priority to International Application No. PCT/GB2009/000624, filed on Mar. 6, 2009, which claims priority to (1) Great Britain Patent Application No. 0804345.7, filed Mar. 7, 2008, and (2) Great Britain Patent Application No. 0821092.4, filed Nov. 18, 2008, each of which is incorporated by reference in its entirety.

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FIELD OF THE DISCLOSURE

This disclosure relates to a process for synthesising cyclic carbonates from epoxides and carbon dioxide using aluminium(salen) complexes as catalysts. The disclosure also provides novel aluminium(salen) complexes, and their synthesis.

BACKGROUND

Cyclic carbonates are commercially important products currently manufactured on a multi-tonne scale for use as polar aprotic solvents, additives, antifoam agents for anti-freeze, plasticisers, and monomers for polymer synthesis (see Darensbourg, et al., *Coord. Chem. Rev.*, 153 (1996), 155-174; Coates, et al., *Angew. Chem. Int. Ed.*, 43 (2004), 6618-6639).

The synthesis of cyclic carbonates generally involves the reaction of epoxides with carbon dioxide, and hence could be used to sequester carbon dioxide, thus reducing the level of greenhouse gases in the atmosphere.

Catalysts for the synthesis of cyclic carbonates from epoxides and carbon dioxide are known in the art (see Darensbourg, et al., *Coord. Chem. Rev.*, 153 (1996), 155-174; Yoshida, et al., *Chem. Eur. J.*, 10 (2004), 2886-2893; Sun, et al., *J. Organomet. Chem.*, 690 (2005), 3490-3497) although these require elevated reaction temperatures and/or high pressures of carbon dioxide, the reaction often being conducted in supercritical carbon dioxide (see Lu, et al., *App. Cat. A*, 234 (2002), 25-33).

Ratzenhofer, et al., (*Angew. Chemie Int. Ed. Engl.*, 19 (1980), 317-318) succeeded in carrying out the reaction between 2-methyloxirane and carbon dioxide at room temperature and atmospheric pressure using catalysts consisting of a mixture of a metal halide and a Lewis base. However, a long reaction time of 7 days was required. Kisch, et al., (*Chem. Ber.*, 119 (1986), 1090-1094), carrying out the same reaction under the same conditions and also using catalysts of this type, reports a reaction time of 3.5 to 93 hours using up to 4 mol % of a ZnCl_2 catalyst and up to 16 mol % of a $(\text{nButyl})_4\text{NI}$ catalyst.

Lu, et al., (*J. Mol. Cat. A*, 210 (2004), 31-34; *J. Cat.*, 227 (2004), 537-541) describe the use of tetradentate Schiff-base aluminium complexes in conjunction with a quaternary ammonium salt or polyether-KY complexes as catalyst sys-

tems for the reaction of various epoxides with carbon dioxide at room temperature and about 6 atmospheres.

Metal(salen) complexes, including aluminium(salen) complexes, are well-known in the art for their use as catalysts. Lu, et al., *App. Cat. A*, 234 (2002), 25-33, describes the use of a monomeric aluminium(salen) catalyst.

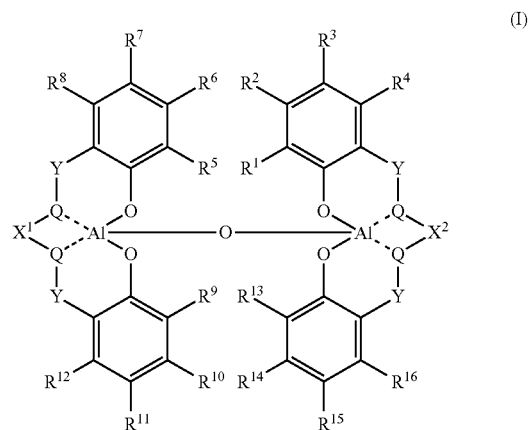
Also known in the art is the method of synthesising aluminium(salen) catalysts by treating a salen ligand with Me_3Al , Et_3Al , Me_2AlCl , Me_2AlOTf , Et_2AlBr or Et_2AlCl in a two-stage process (reviewed in Atwood and Harvey, *Chem. Rev.*, 2001, 101, 37-52).

The present inventor has previously found that, in the presence of a tetraalkylammonium halide cocatalyst, dimeric aluminium(salen) complexes are highly active catalysts for the reaction of epoxides with carbon dioxide to produce cyclic carbonates, and allow the reaction to be carried out at room temperature and atmospheric pressure, using short reaction times and commercially viable amounts of catalyst, as described in Melendez, J., et al., *Eur. J. Inorg. Chem.*, 2007, 3323-3326 and co-pending UK patent application No. 0708016.1, filed 25 Apr. 2007, now published as WO 2008/132474.

SUMMARY

Briefly stated, the disclosed embodiments illustrate a process that incorporates the co-catalyst required in this work into the catalyst molecule, so as to reduce or eliminate the amount of separate components needed. Furthermore, the disclosed embodiments illustrate a process that immobilises the combined catalyst and co-catalyst on a solid support.

Accordingly, a first aspect of a disclosed embodiment provides a dimeric aluminium(salen) catalyst of formula I:



wherein:

Y-Q is $\text{CR}^{\text{C1}}=\text{N}$ or $\text{CR}^{\text{C1}}\text{R}^{\text{C2}}-\text{NR}^{\text{N1}}$, where R^{C1} , R^{C2} and R^{N1} are independently selected from H, halo, optionally substituted C_{1-20} alkyl, optionally substituted C_{5-20} aryl, ether and nitro;

each of the substituents R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , and R^{16} , is independently selected from H, halo, optionally substituted C_{1-20} alkyl (including CAr_3 , where Ar is a C_{5-20} aryl group), optionally substituted C_{5-20} aryl, optionally substituted C_{3-20} heterocycl, ether and nitro;

3

X^1 and X^2 are independently either (i) a C_{2-5} alkylene chain, which is optionally substituted by one or more groups selected from C_{1-4} alkyl and C_{5-7} aryl, or a C_{1-3} bisoxyalkylene chain, which is optionally substituted by one or more groups selected from C_{1-4} alkyl and C_{5-7} aryl or (ii) represent a divalent group selected from C_{5-7} arylene, C_{5-7} cyclic alkylene and C_{3-7} heterocyclylene, which may be optionally substituted;

(i) (a) at least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}$, and R^{16} is selected from L-A, where L is a single bond or a C_{1-10} alkylene group and A is an ammonium group paired with a counterion selected from Cl, Br and I; and/or

(b) at least one of X^1 and X^2 is a divalent C_{3-7} heterocyclylene group, containing a ring atom which is a quaternary nitrogen atom paired with a counterion selected from Cl, Br and I; and/or

(c) at least one of X^1 and X^2 is a C_{2-5} alkylene chain or a C_{1-3} bisoxyalkylene chain, substituted by a group -Q-L-A, where Q is either $-C(=O)-NH-$, or a single bond; and/or

(ii) (a) one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}$, and R^{16} is L-A', where L is as defined above and A' is an ammonium linking group bound to a solid support and paired with a counterion selected from Cl, Br and I; or

(b) one of X^1 and X^2 is a divalent C_{3-7} heterocyclylene group, containing a ring atom which is a quaternary nitrogen forming part of an ammonium linking group bound to a solid support and paired with a counterion selected from Cl, Br and I; or

(c) one of X^1 and X^2 is a C_{2-5} alkylene chain or a C_{1-3} bisoxyalkylene chain, substituted by a group -Q-L-A'.

Thus, when the catalyst is covalently bound to a solid support, only one linking group to the solid support is present. However, one or more ammonium groups/quaternary nitrogen atoms may be present.

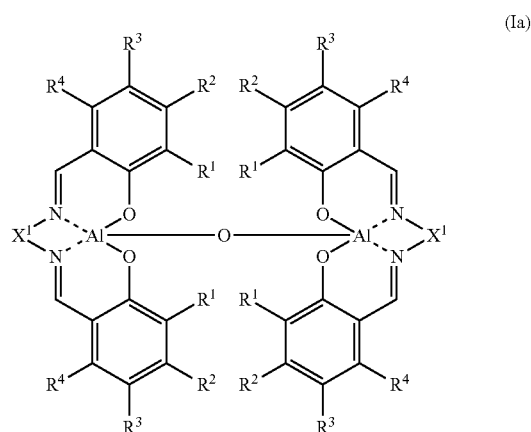
The catalysts of formula I where: (a) at least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}$, and R^{16} is selected from L-A; and/or (b) at least one of X^1 and X^2 is a divalent C_{3-7} heterocyclylene group, containing a ring atom which is a quaternary nitrogen atom paired with a counterion selected from Cl, Br and I; and/or

(c) at least one of X^1 and X^2 is a C_{2-5} alkylene chain or a C_{1-3} bisoxyalkylene chain, substituted by a group -Q-L-A, where Q is either $-C(=O)-$ or a single bond, may be immobilized on a solid support, either by the use of steric effects or by electrostatic binding.

If the catalyst of formula I includes one or more chiral centres, then it may be a (wholly or partially) racemic mixture or other mixture thereof, for example, a mixture enriched in one enantiomer or diastereoisomer, a single enantiomer or diastereoisomer, or a mixture of the stereoisomers. Methods for the preparation (e.g., asymmetric synthesis) and separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner. Preferably the catalyst of formula I is a single enantiomer, if a chiral centre is present.

4

The dimeric aluminium(salen) catalysts of the first aspect may be of formula Ia:



where R^1, R^2, R^3, R^4 and X^1 are as defined above; and

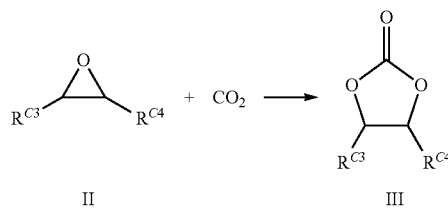
(a) at least one of R^1, R^2, R^3 and R^4 is selected from L-A, where L is a single bond or a C_{1-10} alkylene group and A is an ammonium group paired with a counterion selected from Cl, Br and I; and/or

(b) X^1 is a divalent C_{3-7} heterocyclylene group, containing a ring atom which is a quaternary nitrogen atom paired with a counterion selected from Cl, Br and I; or

(c) X^1 is a C_{2-5} alkylene chain or a C_{1-3} bisoxyalkylene chain, substituted by a group -Q-L-A, where Q is either $-C(=O)-$ or a single bond.

A second aspect of a disclosed embodiment provides a process for the production of cyclic carbonates comprising contacting an epoxide with carbon dioxide in the presence of a dimeric aluminium(salen) catalyst according to the first aspect of a disclosed embodiment.

The reaction of the second aspect may be defined as follows:



wherein R^{C3} and R^{C4} are independently selected from H, optionally substituted C_{1-10} alkyl, optionally substituted C_{3-20} heterocyclyl and optionally substituted C_{5-20} aryl, or R^{C3} and R^{C4} form an optionally substituted linking group between the two carbon atoms to which they are respectively attached. The linking group, together with the carbon atoms to which it is attached, may form an optionally substituted C_{5-20} cycloalkyl or C_{5-20} heterocyclyl group. The C_{5-20} cycloalkyl or C_{5-20} heterocyclyl group may be substituted only in a single position on the ring, for example, adjacent the

5

epoxide. Suitable substituents, include optionally substituted C_{1-10} alkyl, optionally substituted C_{3-20} heterocyclyl and optionally substituted C_{5-20} aryl.

A possible substituent for the C_{1-10} alkyl group is a C_{5-20} aryl group.

The second aspect of a disclosed embodiment also provides the use of a dimeric aluminium(salen) catalyst of the first aspect of a disclosed embodiment for the production of cyclic carbonates from epoxides.

A third aspect of a disclosed embodiment provides a process for the synthesis of a dimeric aluminium(salen) catalyst of formula I.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 shows a flow reactor for use with the disclosed catalysts.

DETAILED DESCRIPTION OF THE EMBODIMENTS

Definitions

Epoxide: The term “epoxide”, as used herein, may pertain to a compound of the formula:



wherein R^{C3} and R^{C4} are independently selected from H, optionally substituted C_{1-10} alkyl, optionally substituted C_{3-20} heterocyclyl and optionally substituted C_{5-20} aryl, or R^{C3} and R^{C4} form an optionally substituted linking group between the two carbon atoms to which they are respectively attached. The linking group, together with the carbon atoms to which it is attached, may form an optionally substituted C_{5-20} cycloalkyl or C_{5-20} heterocyclyl group. The C_{5-20} cycloalkyl or C_{5-20} heterocyclyl group may be substituted only in a single position on the ring, for example, adjacent the epoxide. Suitable substituents, include optionally substituted C_{1-10} alkyl, optionally substituted C_{3-20} heterocyclyl and optionally substituted C_{5-20} aryl.

The optional substituents may be selected from: C_{1-10} alkyl, C_{3-20} heterocyclyl, C_{5-20} aryl, halo, hydroxy, ether, cyano, nitro, carboxy, ester, amido, amino, acylamido, ureido, acyloxy, thiol, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino.

In some embodiments, the C_{1-10} alkyl group is substituted by a C_{5-20} aryl group.

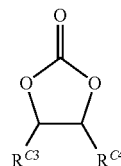
Preferably, the epoxide is a terminal epoxide, i.e. $R^{C4}=H$.

In some embodiments, R^{C3} is selected from optionally substituted C_{1-4} alkyl and optionally substituted C_{5-7} aryl. In some of these embodiments R^{C3} is unsubstituted.

Preferred epoxides are ethylene oxide ($R^{C3}=R^{C4}=H$), propylene oxide ($R^{C3}=\text{methyl}$, $R^{C4}=H$) butylene oxide ($R^{C3}=\text{ethyl}$, $R^{C4}=H$), and styrene oxide ($R^{C3}=\text{phenyl}$, $R^{C4}=H$).

6

Cyclic carbonate: the term “cyclic carbonate”, as used herein, may pertain to a compound of the formula:



wherein R^{C3} and R^{C4} are as defined above.

Solid support: Catalysts of a disclosed embodiment may be immobilized on a solid support by:

- (a) covalent binding (those where one of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , and R^{16} is selected from L-A’);
- (b) steric trapping; or
- (c) electrostatic binding.

These various methods are reviewed by Carlos Baleizão and Hermenegildo Garcia in “Chiral Salen Complexes: An Overview to Recoverable and Reusable Homogeneous and Heterogeneous Catalysts” (*Chem. Rev.* 2006, 106, 3987-4043).

For covalent binding, the solid support needs to contain or be derivatized to contain reactive functionalities which can serve for covalently linking a compound to the surface thereof. Such materials are well known in the art and include, by way of example, silicon dioxide supports containing reactive Si—OH groups, polyacrylamide supports, polystyrene supports, polyethyleneglycol supports, and the like. A further example is sol-gel materials. Silica can be modified to include a 3-chloropropoxy group by treatment with (3-chloropropyl)triethoxysilane. Another example is Al pillared clay, which can also be modified to include a 3-chloropropoxy group by treatment with (3-chloropropyl)triethoxysilane. Such supports will preferably take the form of small beads, pins/crowns, laminar surfaces, pellets or disks. They may also take the form of powders. Solid supports for covalent binding of particular interest in a disclosed embodiment include siliceous MCM-41 and MCM-48 (modified with 3-aminopropyl groups), ITQ-2 and amorphous silica, SBA-15 and hexagonal mesoporous silica. Also of particular interest are sol-gels. Other conventional forms may also be used.

For steric trapping, the most suitable class of solid support is zeolites, which may be natural or modified. The pore size must be sufficiently small to trap the catalyst but sufficiently large to allow the passage of reactants and products to and from the catalyst. Suitable zeolites include zeolites X, Y and EMT as well as those which have been partially degraded to provide mesopores, that allow easier transport of reactants and products.

For the electrostatic binding of the catalyst to a solid support, typical solid supports may include silica, Indian clay, Al-pillared clay, Al-MCM-41, K10, laponite, bentonite, and zinc-aluminum layered double hydroxide. Of these silica and montmorillonite clay are of particular interest.

Alkyl: The term “alkyl”, as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon having from 1 to 20 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic and which may be saturated or unsaturated (e.g. partially saturated, fully unsaturated). Thus, the term “alkyl” includes the sub-classes alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, etc., as discussed below.

Alkylene: The term “alkylene”, as used herein, pertains to a divalent moiety obtained by removing two hydrogen atoms from one or two carbon atoms of a hydrocarbon having from 1 to 20 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic and which may be saturated or unsaturated (e.g. partially saturated, fully unsaturated). Thus, the term “alkylene” includes the sub-classes alkenylene, alkynylene, cycloalkylene, cycloalkenylene, cycloalkynylene, etc., as discussed below.

In the context of alkyl and alkylene groups, the prefixes (e.g. C₁₋₄, C₁₋₇, C₁₋₂₀, C₂₋₇, C₃₋₇, etc.) denote the number of carbon atoms, or the range of number of carbon atoms. For example, the term “C₁₋₄ alkyl”, as used herein, pertains to an alkyl group having from 1 to 4 carbon atoms. Examples of groups of alkyl groups include C₁₋₄ alkyl (“lower alkyl”), C₁₋₇ alkyl and C₁₋₂₀ alkyl. Note that the first prefix may vary according to other limitations; for example, for unsaturated alkyl groups, the first prefix must be at least 2; for cyclic alkyl groups, the first prefix must be at least 3; etc. For example, the term “C₁₋₇ alkylene”, as used herein, pertains to an alkylene group having from 1 to 7 carbon atoms.

Examples of (unsubstituted) saturated alkyl groups include, but are not limited to, methyl (C₁), ethyl (C₂), propyl (C₃), butyl (C₄), pentyl (C₅), hexyl (C₆), and heptyl (C₇).

Examples of (unsubstituted) saturated linear alkyl groups include, but are not limited to, methyl (C₁), ethyl (C₂), n-propyl (C₃), n-butyl (C₄), n-pentyl (amyl) (C₅), n-hexyl (C₆), and n-heptyl (C₇).

Examples of (unsubstituted) saturated branched alkyl groups include iso-propyl (C₃), iso-butyl (C₄), sec-butyl (C₄), tert-butyl (C₄), iso-pentyl (C₅), and neo-pentyl (C₅).

Examples of (unsubstituted) saturated alkylene groups include, but are not limited to, methylene (C₁), ethylene (C₂), propylene (C₃), butylene (C₄), pentylene (C₅), hexylene (C₆), and heptylene (C₇).

Examples of (unsubstituted) saturated linear alkylene groups include, but are not limited to, methylene (C₁), ethylene (C₂), n-propylene (C₃), n-butylene (C₄), n-pentylene (amylene) (C₅), n-hexylene (C₆), and n-heptylene (C₇).

Examples of (unsubstituted) saturated branched alkyl groups include iso-propylene (C₃), iso-butylene (C₄), sec-butylene (C₄), tert-butylene (C₄), iso-pentylene (C₅), and neo-pentylene (C₅).

Alkenyl: The term “alkenyl”, as used herein, pertains to an alkyl group having one or more carbon-carbon double bonds. Examples of groups of alkenyl groups include C₂₋₄ alkenyl, C₂₋₇ alkenyl, C₂₋₂₀ alkenyl.

Examples of (unsubstituted) unsaturated alkenyl groups include, but are not limited to, ethenyl (vinyl, —CH=CH₂), 1-propenyl (—CH=CH—CH₃), 2-propenyl (allyl, —CH₂—CH=CH₂), isopropenyl (1-methylvinyl, —C(CH₃)=CH₂), butenyl (C₄), pentenyl (C₅), and hexenyl (C₆).

Alkenylene: The term “alkenylene”, as used herein, pertains to an alkylene group having one or more carbon-carbon double bonds. Examples of groups of alkenylene groups include C₂₋₄ alkenylene, C₂₋₇ alkenylene, C₂₋₂₀ alkenylene.

Alkynyl: The term “alkynyl”, as used herein, pertains to an alkyl group having one or more carbon-carbon triple bonds. Examples of groups of alkynyl groups include C₂₋₄ alkynyl, C₂₋₇ alkynyl, C₂₋₂₀ alkynyl.

Examples of (unsubstituted) unsaturated alkynyl groups include, but are not limited to, ethynyl (ethinyl, —C≡CH) and 2-propynyl (propargyl, —CH₂—C≡CH).

Alkynylene: The term “alkynylene”, as used herein, pertains to an alkylene group having one or more carbon-carbon triple bonds. Examples of groups of alkynylene groups include C₂₋₄ alkynylene, C₂₋₇ alkynylene, C₂₋₂₀ alkynylene.

Cycloalkyl: The term “cycloalkyl”, as used herein, pertains to an alkyl group which is also a cyclyl group; that is, a monovalent moiety obtained by removing a hydrogen atom from an alicyclic ring atom of a carbocyclic ring of a carbocyclic compound, which carbocyclic ring may be saturated or unsaturated (e.g. partially unsaturated, fully unsaturated), which moiety has from 3-20 carbon atoms (unless otherwise specified), including from 3 to 20 ring atoms. Thus, the term “cycloalkyl” includes the sub-classes cycloalkenyl and cycloalkynyl. Preferably, each ring has from 3 to 7 ring atoms. Examples of groups of cycloalkyl groups include C₃₋₂₀ cycloalkyl, C₃₋₁₅ cycloalkyl, C₃₋₁₀ cycloalkyl, C₃₋₇ cycloalkyl.

Cycloalkylene: The term “cycloalkylene”, as used herein, pertains to an alkylene group which is also a cyclyl group; that is, a divalent moiety obtained by removing two hydrogen atoms from one or two alicyclic ring atoms of a carbocyclic ring of a carbocyclic compound, which carbocyclic ring may be saturated or unsaturated (e.g. partially unsaturated, fully unsaturated), which moiety has from 3-20 carbon atoms (unless otherwise specified), including from 3 to 20 ring atoms. Thus, the term “cycloalkylene” includes the sub-classes cycloalkenylene and cycloalkynylene. Preferably, each ring has from 3 to 7 ring atoms. Examples of groups of cycloalkylene groups include C₃₋₂₀ cycloalkylene, C₃₋₁₅ cycloalkylene, C₃₋₁₀ cycloalkylene, C₃₋₇ cycloalkylene.

Cyclic alkylene: The term “cyclic alkylene” as used herein pertains to a divalent moiety obtained by removing a hydrogen atom from each of two adjacent alicyclic ring atoms of a carbocyclic ring of a carbocyclic compound, which carbocyclic ring may be saturated or unsaturated (e.g. partially saturated, fully unsaturated), which moiety has from 3 to 20 carbon atoms (unless otherwise specified), including from 3 to 20 ring atoms. Preferably each ring has from 5 to 7 ring atoms. Examples of groups of cyclic alkylene groups include C₃₋₂₀ cyclic alkylene, C₃₋₁₅ cyclic alkylene, C₃₋₁₀ cyclic alkylene, C₃₋₇ cyclic alkylene.

Examples of cycloalkyl groups and cyclic alkylene groups include, but are not limited to, those derived from:

saturated monocyclic hydrocarbon compounds: cyclopropane (C₃), cyclobutane (C₄), cyclopentane (C₅), cyclohexane (C₆), cycloheptane (C₇), methylcyclopropane (C₄), dimethylcyclopropane (C₅), methylcyclobutane (C₅), dimethylcyclobutane (C₆), methylcyclopentane (C₆), dimethylcyclopentane (C₇), methylcyclohexane (C₇), dimethylcyclohexane (C₈), menthane (C₁₀);

unsaturated monocyclic hydrocarbon compounds: cyclopropene (C₃), cyclobutene (C₄), cyclopentene (C₅), cyclohexene (C₆), methylcyclopropene (C₄), dimethylcyclopropene (C₅), methylcyclobutene (C₅), dimethylcyclobutene (C₆), methylcyclopentene (C₆), dimethylcyclopentene (C₇), methylcyclohexene (C₇), dimethylcyclohexene (C₈);

saturated polycyclic hydrocarbon compounds: thujane (C₁₀), carane (C₁₀), pinane (C₁₀), bornane (C₁₀), norcarane (C₇), norpinane (C₇), norbornane (C₇), adamantane (C₁₀), decalin (decahydronaphthalene) (C₁₀);

unsaturated polycyclic hydrocarbon compounds: camphene (C₁₀), limonene (C₁₀), pinene (C₁₀);

polycyclic hydrocarbon compounds having an aromatic ring:

indene (C₉), indane (e.g., 2,3-dihydro-1H-indene) (C₉), tetralin (1,2,3,4-tetrahydronaphthalene) (C₁₀), acenaphthene (C₁₂), fluorene (C₁₃), phenalene (C₁₃), acephenanthrene (C₁₅), aceanthrene (C₁₆), cholanthrene (C₂₀).

Heterocyclyl: The term “heterocyclyl”, as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound,

which moiety has from 3 to 20 ring atoms (unless otherwise specified), of which from 1 to 10 are ring heteroatoms. Preferably, each ring has from 3 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms.

Heterocyclylene: The term “heterocyclylene”, as used herein, pertains to a divalent moiety obtained by removing a hydrogen atom from each of two adjacent ring atoms of a heterocyclic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified), of which from 1 to 10 are ring heteroatoms. Preferably, each ring has from 3 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms.

The heterocyclyl or heterocyclylene group may be bonded via carbon or hetero ring atoms. Preferably, the heterocyclylene group is bonded via two carbon atoms.

When referring to heterocyclyl or heterocyclylene groups, the prefixes (e.g. C₃₋₂₀, C₃₋₇, C₅₋₆, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term “C₅₋₆ heterocyclyl”, as used herein, pertains to a heterocyclyl group having 5 or 6 ring atoms. Examples of groups of heterocyclyl groups include C₃₋₂₀ heterocyclyl, C₅₋₂₀ heterocyclyl, C₃₋₁₅ heterocyclyl, C₅₋₁₅ heterocyclyl, C₃₋₁₂ heterocyclyl, C₅₋₁₂ heterocyclyl, C₃₋₁₀ heterocyclyl, C₅₋₁₀ heterocyclyl, C₃₋₇ heterocyclyl, C₅₋₇ heterocyclyl, and C₅₋₆ heterocyclyl.

Similarly, the term “C₅₋₆ heterocyclylene”, as used herein, pertains to a heterocyclylene group having 5 or 6 ring atoms. Examples of groups of heterocyclylene groups include C₃₋₂₀ heterocyclylene, C₅₋₂₀ heterocyclylene, C₃₋₁₅ heterocyclylene, C₅₋₁₅ heterocyclylene, C₃₋₁₂ heterocyclylene, C₅₋₁₂ heterocyclylene, C₃₋₁₀ heterocyclylene, C₅₋₁₀ heterocyclylene, C₃₋₇ heterocyclylene, C₅₋₇ heterocyclylene, and C₅₋₆ heterocyclylene.

Examples of monocyclic heterocyclyl and heterocyclylene groups include, but are not limited to, those derived from:

N₁: aziridine (C₃), azetidine (C₄), pyrrolidine (tetrahydropyrrole) (C₅), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C₅), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C₅), piperidine (C₆), dihydropyridine (C₆), tetrahydropyridine (C₆), azepine (C₇);

O₁: oxirane (C₃), oxetane (C₄), oxolane (tetrahydrofuran) (C₅), oxole (dihydrofuran) (C₅), oxane (tetrahydropyran) (C₆), dihydropyran (C₆), pyran (C₆), oxepin (C₇);

S₁: thiirane (C₃), thietane (C₄), thiolane (tetrahydrothiophene) (C₅), thiane (tetrahydrothiopyran) (C₆), thiopane (C₇);

O₂: dioxolane (C₅), dioxane (C₆), and dioxepane (C₇);

O₃: trioxane (C₆);

N₂: imidazolidine (C₅), pyrazolidine (diazolidine) (C₅), imidazoline (C₅), pyrazoline (dihydropyrazole) (C₅), piperazine (C₆);

N₁O₁: tetrahydrooxazole (C₅), dihydrooxazole (C₅), tetrahydroisoxazole (C₅), dihydroisoxazole (C₅), morpholine (C₆), tetrahydrooxazine (C₆), dihydrooxazine (C₆), oxazine (C₆);

N₁S₁: thiazoline (C₅), thiazolidine (C₅), thiomorpholine (C₆);

N₂O₁: oxadiazine (C₆);

O₁S₁: oxathiole (C₅) and oxathiane (thioxane) (C₆); and,

N₁O₁S₁: oxathiazine (C₆).

Examples of substituted (non-aromatic) monocyclic heterocyclyl and heterocyclylene groups include those derived from saccharides, in cyclic form, for example, furanoses (C₅), such as arabinofuranose, lyxofuranose, ribofuranose, and xylofuranose, and pyranoses (C₆), such as allopyranose, altropyranose, glucopyranose, mannopyranose, gulopyranose, idopyranose, galactopyranose, and talopyranose.

C₅₋₂₀ aryl: The term “C₅₋₂₀ aryl”, as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of a C₅₋₂₀ aromatic compound, said compound having one ring, or two or more rings (e.g., fused), and having from 5 to 20 ring atoms, and wherein at least one of said ring(s) is an aromatic ring. Preferably, each ring has from 5 to 7 carbon atoms.

The ring atoms may be all carbon atoms, as in “carboaryl groups” in which case the group may conveniently be referred to as a “C₅₋₂₀ carboaryl” group.

C₅₋₂₀ arylene: The term “C₅₋₂₀ arylene”, as used herein, pertains to a divalent moiety obtained by removing a hydrogen atom from each of two adjacent ring atoms of a C₅₋₂₀ aromatic compound, said compound having one ring, or two or more rings (e.g., fused), and having from 5 to 20 ring atoms, and wherein at least one of said ring(s) is an aromatic ring. Preferably, each ring has from 5 to 7 carbon atoms.

The ring atoms may be all carbon atoms, as in “carboarylene groups” in which case the group may conveniently be referred to as a “C₅₋₂₀ carboarylene” group.

Examples of C₅₋₂₀ aryl and C₅₋₂₀ arylene groups which do not have ring heteroatoms (i.e. C₅₋₂₀ carboaryl and C₅₋₂₀ carboarylene groups) include, but are not limited to, those derived from benzene (i.e. phenyl) (C₆), naphthalene (C₁₀), anthracene (C₁₄), phenanthrene (C₁₄), and pyrene (C₁₆).

Alternatively, the ring atoms may include one or more heteroatoms, including but not limited to oxygen, nitrogen, and sulfur, as in “heteroaryl groups” or “heteroarylene groups”. In this case, the group may conveniently be referred to as a “C₅₋₂₀ heteroaryl” or “C₅₋₂₀ heteroarylene” group, wherein “C₅₋₂₀” denotes ring atoms, whether carbon atoms or heteroatoms. Preferably, each ring has from 5 to 7 ring atoms, of which from 0 to 4 are ring heteroatoms.

The heteroaryl or heteroarylene group may be bonded via carbon or hetero ring atoms. Preferably, the heteroarylene group is bonded via two carbon atoms.

Examples of C₅₋₂₀ heteroaryl and C₅₋₂₀ heteroarylene groups include, but are not limited to, C₅ heteroaryl and C₅ heteroarylene groups derived from furan (oxole), thiophene (thiole), pyrrole (azole), imidazole (1,3-diazole), pyrazole (1,2-diazole), triazole, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, tetrazole and oxatriazole; and C₆ heteroaryl groups derived from isoxazine, pyridine (azine), pyridazine (1,2-diazine), pyrimidine (1,3-diazine; e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) and triazine.

Examples of C₅₋₂₀ heteroaryl and C₅₋₂₀ heteroarylene groups which comprise fused rings, include, but are not limited to, C₉ heteroaryl and C₉ heteroarylene groups derived from benzofuran, isobenzofuran, benzothiophene, indole, isoindole; C₁₀ heteroaryl and C₁₀ heteroarylene groups derived from quinoline, isoquinoline, benzodiazine, pyridopyridine; C₁₄ heteroaryl and C₁₄ heteroarylene groups derived from acridine and xanthene.

Bisoxyc₁₋₃ alkylene: —O—(CH₂)_m—O—, where m is 1 to 3.

The above alkyl, alkylene, cyclic alkylene, bisoxyalkylene, heterocyclyl, heterocyclylene, aryl, and arylene groups, whether alone or part of another substituent, may themselves optionally be substituted with one or more groups selected from themselves and the additional substituents listed below.

Halo: —F, —Cl, —Br, and —I.

Hydroxy: —OH.

Ether: —OR, wherein R is an ether substituent, for example, a C₁₋₇ alkyl group (also referred to as a C₁₋₇ alkoxy group), a C₃₋₂₀ heterocyclyl group (also referred to as a C₃₋₂₀ heterocycloxy group), or a C₅₋₂₀ aryl group (also referred to as a C₅₋₂₀ aryloxy group), preferably a C₁₋₇ alkyl group.

Nitro: —NO₂.

Cyano (nitrile, carbonitrile): —CN.

11

Acyl (keto): $-\text{C}(=\text{O})\text{R}$, wherein R is an acyl substituent, for example, H, a C_{1-7} alkyl group (also referred to as C_{1-7} alkylacyl or C_{1-7} alkanoyl), a C_{3-20} heterocyclyl group (also referred to as C_{3-20} heterocyclylacyl), or a C_{5-20} aryl group (also referred to as C_{5-20} arylacyl), preferably a C_{1-7} alkyl group. Examples of acyl groups include, but are not limited to, $-\text{C}(=\text{O})\text{CH}_3$ (acetyl), $-\text{C}(=\text{O})\text{CH}_2\text{CH}_3$ (propionyl), $-\text{C}(=\text{O})\text{C}(\text{CH}_3)_3$ (pivaloyl), and $-\text{C}(=\text{O})\text{Ph}$ (benzoyl, phenone).

Carboxy (carboxylic acid): $-\text{COOH}$.

Ester (carboxylate, carboxylic acid ester, oxycarbonyl): $-\text{C}(=\text{O})\text{OR}$, wherein R is an ester substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of ester groups include, but are not limited to, $-\text{C}(=\text{O})\text{OCH}_3$, $-\text{C}(=\text{O})\text{OCH}_2\text{CH}_3$, $-\text{C}(=\text{O})\text{OC}(\text{CH}_3)_3$, and $-\text{C}(=\text{O})\text{OPh}$.

Amido (carbamoyl, carbamyl, aminocarbonyl, carboxamide): $-\text{C}(=\text{O})\text{NR}^1\text{R}^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{NHCH}_3$, $-\text{C}(=\text{O})\text{N}(\text{CH}_3)_2$, $-\text{C}(=\text{O})\text{NHCH}_2\text{CH}_3$, and $-\text{C}(=\text{O})\text{N}(\text{CH}_2\text{CH}_3)_2$, as well as amido groups in which R^1 and R^2 , together with the nitrogen atom to which they are attached, form a heterocyclic structure as in, for example, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, and piperazinylcarbonyl.

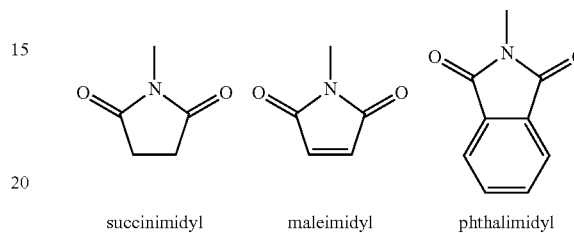
Amino: $-\text{NR}^1\text{R}^2$, wherein R^1 and R^2 are independently amino substituents, for example, hydrogen, a C_{1-7} alkyl group (also referred to as C_{1-7} alkylamino or di- C_{1-7} alkylamino), a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably H or a C_{1-7} alkyl group, or, in the case of a "cyclic" amino group, R^1 and R^2 , taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Examples of amino groups include, but are not limited to, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHCH}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_3)_2$, and $-\text{NHPh}$. Examples of cyclic amino groups include, but are not limited to, aziridinyl, azetidiny, pyrrolidinyl, piperidino, piperazinyl, perhydropyridazepinyl, morpholino, and thiomorpholino. In particular, the cyclic amino groups may be substituted on their ring by any of the substituents defined here, for example carboxy, carboxylate and amido.

Ammonium: $-\text{NR}^{\text{N}1}\text{R}^{\text{N}2}\text{R}^{\text{N}3}$, wherein $\text{R}^{\text{N}1}$, $\text{R}^{\text{N}2}$ and $\text{R}^{\text{N}3}$ are independently ammonium substituents, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group and where one or two of $\text{R}^{\text{N}1}$, $\text{R}^{\text{N}2}$ and $\text{R}^{\text{N}3}$ may also be H. One of $\text{R}^{\text{N}1}$, $\text{R}^{\text{N}2}$ and $\text{R}^{\text{N}3}$ may be a C_{1-3} alkoxy ($-(\text{CH}_2)_{1-3}-\text{OH}$) group. Two or three of the ammonium substituents may join together to form cyclic or cage-like structures. Examples of ammonium groups include, but are not limited to, $-\text{NH}(\text{CH}_3)_2$, $-\text{NH}(\text{CH}(\text{CH}_3)_2)_2$, $-\text{N}(\text{CH}_3)_3$, $-\text{N}(\text{CH}_2\text{CH}_3)_3$, and $-\text{NH}_2\text{Ph}$.

Ammonium linking group: $-\text{NR}^{\text{N}1}\text{R}^{\text{N}2}\text{R}^{\text{N}4}-$, wherein $\text{R}^{\text{N}1}$ and $\text{R}^{\text{N}2}$ are independently ammonium substituents, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group and where one or both of $\text{R}^{\text{N}1}$ and $\text{R}^{\text{N}2}$ may also be H. The two ammonium substituents may join together to form a cyclic structure. $\text{R}^{\text{N}4}$ is a divalent ammonium substituent, for example, a C_{1-7} alkylene group, a C_{3-20} heterocyclylene group, or a C_{5-20} arylene group or a divalent C_{1-3} alkoxy ($-(\text{CH}_2)_{1-3}-\text{O}-$) group. Examples of ammonium linking groups include, but are not limited to, $-\text{NH}(\text{CH}_3)(\text{CH}_2)-$, $-\text{NH}(\text{CH}(\text{CH}_3)_2)(\text{C}(\text{CH}_3)_2)-$, $-\text{N}(\text{CH}_3)_2(\text{CH}_2)-$, $-\text{N}(\text{CH}_2\text{CH}_3)_2(\text{CH}_2\text{CH}_2)-$, and $-\text{NHPh}(\text{CH}_2)-$.

12

Acylamido (acylamino): $-\text{NR}^1\text{C}(=\text{O})\text{R}^2$, wherein R^1 is an amide substituent, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably H or a C_{1-7} alkyl group, most preferably H, and R^2 is an acyl substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of acylamide groups include, but are not limited to, $-\text{NHC}(=\text{O})\text{CH}_3$, $-\text{NHC}(=\text{O})\text{CH}_2\text{CH}_3$, and $-\text{NHC}(=\text{O})\text{Ph}$. R^1 and R^2 may together form a cyclic structure, as in, for example, succinimidyl, maleimidyl, and phthalimidyl:



Ureido: $-\text{N}(\text{R}^1)\text{CONR}^2\text{R}^3$ wherein R^2 and R^3 are independently amino substituents, as defined for amino groups, and R^1 is a ureido substituent, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably hydrogen or a C_{1-7} alkyl group. Examples of ureido groups include, but are not limited to, $-\text{NHCONH}_2$, $-\text{NHCONHMe}$, $-\text{NHCONHEt}$, $-\text{NHCONMe}_2$, $-\text{NHCONEt}_2$, $-\text{NMeCONH}_2$, $-\text{NMeCONHMe}$, $-\text{NMeCONHEt}$, $-\text{NMeCONMe}_2$, $-\text{NMeCONEt}_2$ and $-\text{NHCONHPh}$.

Acyloxy (reverse ester): $-\text{OC}(=\text{O})\text{R}$, wherein R is an acyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of acyloxy groups include, but are not limited to, $-\text{OC}(=\text{O})\text{CH}_3$ (acetoxy), $-\text{OC}(=\text{O})\text{CH}_2\text{CH}_3$, $-\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$, $-\text{OC}(=\text{O})\text{Ph}$, $-\text{OC}(=\text{O})\text{C}_6\text{H}_4\text{F}$, and $-\text{OC}(=\text{O})\text{CH}_2\text{Ph}$.

Thiol: $-\text{SH}$.

Thioether (sulfide): $-\text{SR}$, wherein R is a thioether substituent, for example, a C_{1-7} alkyl group (also referred to as a C_{1-7} alkylthio group), a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of C_{1-7} alkylthio groups include, but are not limited to, $-\text{SCH}_3$ and $-\text{SCH}_2\text{CH}_3$.

Sulfoxide (sulfinyl): $-\text{S}(=\text{O})\text{R}$, wherein R is a sulfoxide substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfoxide groups include, but are not limited to, $-\text{S}(=\text{O})\text{CH}_3$ and $-\text{S}(=\text{O})\text{CH}_2\text{CH}_3$.

Sulfonyl (sulfone): $-\text{S}(=\text{O})_2\text{R}$, wherein R is a sulfone substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfone groups include, but are not limited to, $-\text{S}(=\text{O})_2\text{CH}_3$ (methanesulfonyl, mesyl), $-\text{S}(=\text{O})_2\text{CF}_3$, $-\text{S}(=\text{O})_2\text{CH}_2\text{CH}_3$, and 4-methylphenylsulfonyl (tosyl).

Thioamido (thiocarbamyl): $-\text{C}(=\text{S})\text{NR}^1\text{R}^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of thioamido groups include, but are not limited to, $-\text{C}(=\text{S})\text{NH}_2$, $-\text{C}(=\text{S})\text{NHCH}_3$, $-\text{C}(=\text{S})\text{N}(\text{CH}_3)_2$, and $-\text{C}(=\text{S})\text{NHCH}_2\text{CH}_3$.

Sulfonamino: $-\text{NR}^1\text{S}(=\text{O})_2\text{R}$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfonamino substituent, for example, a C_{1-7} alkyl group, a

C₃₋₂₀heterocyclyl group, or a C₅₋₂₀aryl group, preferably a C₁₋₇alkyl group. Examples of sulfonamino groups include, but are not limited to, —NHS(=O)₂CH₃, —NHS(=O)₂Ph and —N(CH₃)S(=O)₂C₆H₅.

As mentioned above, the groups that form the above listed substituent groups, e.g. C₁₋₇ alkyl, C₃₋₂₀ heterocyclyl and C₅₋₂₀ aryl, may themselves be substituted. Thus, the above definitions cover substituent groups which are substituted.

C₁₋₃ alkylene: —(CH₂)_m—, where m is 1 to 3.

Chemically Protected Forms

It may be convenient or desirable to prepare, purify, handle and/or use the active compound in a chemically protected form. The term “chemically protected form” is used herein in the conventional chemical sense and pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions under specified conditions (e.g., pH, temperature, radiation, solvent, and the like). In practice, well known chemical methods are employed to reversibly render unreactive a functional group, which otherwise would be reactive, under specified conditions. In a chemically protected form, one or more reactive functional groups are in the form of a protected or protecting group (also known as a masked or masking group or a blocked or blocking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, *Protective Groups in Organic Synthesis* (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

Unless otherwise specified, a reference to a particular compound also includes chemically protected forms thereof.

A wide variety of such “protecting,” “blocking,” or “masking” methods are widely used and well known in organic synthesis. For example, a compound which has two non-equivalent reactive functional groups, both of which would be reactive under specified conditions, may be derivatized to render one of the functional groups “protected,” and therefore unreactive, under the specified conditions; so protected, the compound may be used as a reactant which has effectively only one reactive functional group. After the desired reaction (involving the other functional group) is complete, the protected group may be “deprotected” to return it to its original functionality.

For example, a hydroxy group may be protected as an ether (—OR) or an ester (—OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (—OC(=O)CH₃, —OAc).

For example, an aldehyde or ketone group may be protected as an acetal (R—CH(OR)₂) or ketal (R₂C(OR)₂), respectively, in which the carbonyl group (>C=O) is converted to a diether (>C(OR)₂), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

For example, an amine group may be protected, for example, as an amide (—NRCO—R) or a urethane (—NRCO—OR), for example, as: a methyl amide (—NHCO—CH₃); a benzyloxy amide (—NHCO—OCH₂C₆H₅, —NH-Cbz); as a t-butoxy amide (—NHCO—OC(CH₃)₃, —NH-Boc); a 2-biphenyl-2-propoxy amide (—NHCO—OC(CH₃)₂C₆H₄C₆H₅, —NH-Bpoc), as a 9-fluorenylmethoxy amide (—NH-Fmoc), as a 6-nitroveratryloxy amide (—NH-Nvoc), as a 2-trimethylsilylethoxy amide (—NH-Teoc), as a 2,2,2-trichloroethoxy amide (—NH-Troc), as an allyloxy amide (—NH-Alloc), as a

2(-phenylsulphonyl)ethoxy amide (—NH-Psec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical (>N—O.).

For example, a carboxylic acid group may be protected as an ester for example, as: a C₁₋₇alkyl ester (e.g., a methyl ester; a t-butyl ester); a C₁₋₇haloalkyl ester (e.g., a C₁₋₇trihaloalkyl ester); a triC₁₋₇alkylsilyl-C₁₋₇alkyl ester; or a C₅₋₂₀aryl-C₁₋₇alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

For example, a thiol group may be protected as a thioether (—SR), for example, as: a benzyl thioether; an acetamidomethyl ether (—S—CH₂NHC(=O)CH₃).

In particular application in a disclosed embodiment is the protection of hydroxy and amino groups.

Catalysed Reactions

In one aspect of a disclosed embodiment, there is provided a process for the production of cyclic carbonates comprising contacting an epoxide with carbon dioxide in the presence of a dimeric aluminium(salen) catalyst of formula I.

This reaction has the advantage that it may be carried out at easily accessible temperatures of between 0 and 40° C. and pressures of between 0.5 and 2 atm. The reaction may even be carried out at temperatures of between 0 and 140° C. and pressures of between 0.5 and 5 atm. Preferably, the reaction temperature lies between 20 and 30° C. Yields of over 50% may be achieved with short reaction times of 3 to 24 hours, using commercially viable amounts of catalyst, that is, from 0.1 to 10 mol %, preferably 0.1 to 2.5 mol %. In some cases, yields of over 70% or over 90% may be achieved under these conditions.

The reaction may also be carried out in a flow reactor, wherein the reaction is continuous.

In some embodiments, the carbon dioxide may be supplied heated, and in other embodiments, the reaction may be heated by a conventional or microwave system.

Catalysts

The embodiments and preferences expressed below may be combined with one another, where appropriate.

In some aspects of a disclosed embodiment, L is selected from a single bond and C₁₋₇ alkylene.

In some aspects of a disclosed embodiment, the aluminium (salen) catalyst of formula I is symmetrical, such that X¹=X², R¹=R¹³, R²=R¹⁴, R³=R¹⁵, R⁴=R¹⁶, R⁵=R⁹, R⁶=R¹⁰, R⁷=R¹¹, and R⁸=R¹². More preferably R¹, R⁵, R⁹, and R¹³ are identical, R², R⁶, R¹⁰ and R¹⁴ are identical, R³, R⁷, R¹¹, and R¹⁵ are identical, and R⁴, R⁸, R¹² and R¹⁶ are identical. Such catalysts are of formula Ia, which may be preferred.

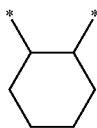
If the catalyst is bound to a solid support, then it will not be fully symmetrical.

In some embodiments, X¹ and X² are the same.

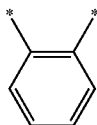
In some embodiments, X¹ and X² are independently selected from a C₂₋₅ alkylene chain, which is preferably unsubstituted, and a C₁₋₃ bisoxylakylene chain, which is preferably unsubstituted. These groups can be represented as —(CH₂)_n— or —O—(CH₂)_p—O—, where n is 2, 3, 4, or 5 and p is 1, 2, or 3. In these embodiments, n is preferably 2 or 3 and p is preferably 1 or 2. n is more preferably 2. In these embodiments X¹ and X² are preferably selected from —(CH₂)_n— (e.g. —C₂H₄—).

In other embodiments, X¹ and X² independently represent a divalent group selected from C₅₋₇ arylene, C₅₋₇ cyclic alkylene and C₃₋₇ heterocyclylene, which may be optionally substituted. Preferably X¹ and X² independently represent C₅₋₇ cyclic alkylene, and more preferably C₆ cyclic alkylene. This group is preferably saturated, and therefore is the group:

15



In other preferred embodiments, X^1 and X^2 independently represent C_{5-7} arylene, which is more preferably C_6 arylene, and in particular, benzylenes:



When X^1 and X^2 independently represent a divalent group selected from C_{5-7} arylene, C_{5-7} cyclic alkylene and C_{3-7} heterocyclene, it may preferably be unsubstituted. If it is substituted, then the substituents may be selected from nitro, halo, C_{1-4} alkyl, including substituted C_{1-4} alkyl, (e.g. methyl, benzyl), C_{1-4} alkoxy (e.g. methoxy) and hydroxy.

Preferably Y-Q is $CR^{C1}=N$, wherein R^{C1} is as defined above. R^{C1} is preferably selected from H and C_{1-4} alkyl. More preferably Y-Q is $CH=N$.

If Y-Q is $CR^{C1}R^{C2}-NR^{N1}$, then in some embodiments R^{C1} , R^{C2} and R^{N1} are H

Preferably $R^4=R^8=R^{12}=R^{16}=H$.

In some embodiments, $R^1=R^5=R^9=R^{13}=H$.

In some embodiments, it is one or more of R^3 , R^7 , R^{11} and R^{15} that is -L-A or L-A'. In some of these embodiments, if one of these groups is -L-A', the other groups are -L-

A. Alternatively, the other groups may be -L-A^M, where A^M is a tertiary amine group, i.e. an amino group where the amino substituents are both not hydrogen, for example, C_{1-7} alkyl (ethyl). The L in all these groups may be the same.

Preferably those of R^1 , R^2 , R^3 , R^5 , R^6 , R^7 , R^9 , R^{10} , R^{11} , R^{13} , R^{14} , R^{15} and R^{16} which do not comprise -L-A or -L-A' are independently selected from H, C_{1-7} alkyl, ether and nitro.

If a group selected from R^1 , R^2 , R^3 , R^5 , R^6 , R^7 , R^9 , R^{10} , R^{11} , R^{13} , R^{14} , R^{15} and R^{16} is ether, then the ether group is preferably a C_{1-7} alkoxy group and more preferably C_{1-4} alkoxy group, e.g. methoxy.

If a group selected from R^1 , R^2 , R^3 , R^5 , R^6 , R^7 , R^9 , R^{10} , R^{11} , R^{13} , R^{14} , and R^{15} is C_{1-7} alkyl, it is preferably butyl, more preferably tert-butyl.

L is preferably unsubstituted.

L may preferably be a C_{1-3} alkylene group, e.g. methylene, ethylene, propylene, and in some embodiments is methylene.

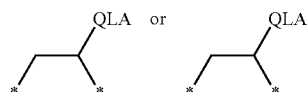
A may preferably be selected from ammonium groups where R^{N1} , R^{N2} and R^{N3} are independently selected from C_{1-7} alkyl groups and C_{5-20} aryl groups, and where one or two of R^{N1} , R^{N2} and R^{N3} may also be H. Ammonium groups of particular interest in a disclosed embodiment include, but are not limited to, $-NH(CH_3)_2$, $-NH(CH(CH_3)_2)_2$, $-N(CH_3)_3$, $-N(CH_2CH_3)_3$, and $-NH_2Ph$.

A' may preferably be selected from ammonium linking groups where R^{N1} and R^{N2} are independently selected from C_{1-7} alkyl groups and C_{5-20} aryl groups, where one or both of R^{N1} and R^{N2} may also be H and where R^{N4} is a C_{1-7} alkylene group. Ammonium linking groups of particular interest in a disclosed embodiment include, but are not limited to, $-NH(CH_3)(CH_2)-$, $-NH(CH(CH_3)_2)(C(CH_3)_2)-$, $-N(CH_3)_2(CH_2)-$, $-N(CH_2CH_3)_2(CH_2CH_2)-$, and $-NHPh(CH_2)-$.

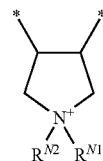
16

In some embodiments, Q may be $-C(=O)-O-$ or $-C(=O)-NH-$.

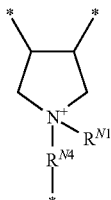
When X^1 and/or X^2 is substituted by -Q-L-A or -Q-L-A', it is preferably a C_2 or C_3 alkylene group, more preferably a C_2 alkylene group, and may be of the formula:



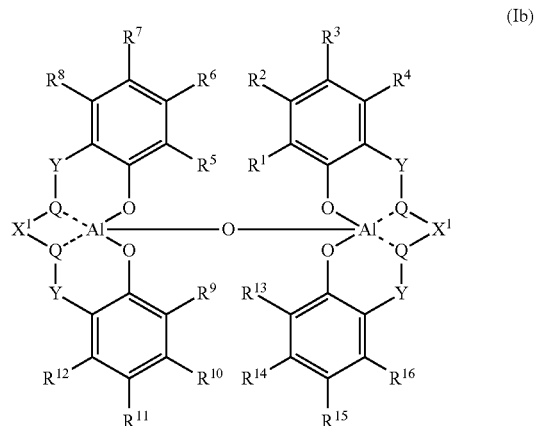
If X^1 or X^2 is a divalent C_{3-7} heterocyclene group containing a ring atom which is a quaternary nitrogen atom, then it is preferably of the formula:



If X^1 or X^2 is a divalent C_{3-7} heterocyclene group containing a ring atom which is a quaternary nitrogen forming part of an ammonium linking group, then it is preferably of the formula:



In some aspects of a disclosed embodiment, the catalyst is of formula Ib:



wherein:

Y-Q is $CR^{C1}=N$ or $CR^{C1}R^{C2}-NR^{N1}$, where R^{C1} , R^{C2} and R^{N1} are independently selected from H, halo, optionally substituted C_{1-20} alkyl, optionally substituted C_{5-20} aryl, ether and nitro;

each of the substituents R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , and R^{16} , is independently

17

selected from H, halo, optionally substituted C_{1-20} alkyl (including CAr_3 , where Ar is a C_{5-20} aryl group), optionally substituted C_{5-20} aryl, optionally substituted C_{3-20} heterocycl, ether and nitro;

X is either of the formula $-(CH_2)_n-$ or $-O-(CH_2)_p-$ O—, where n is 2, 3, 4, or 5 and p is 1, 2, or 3, or represents a divalent group selected from C_{5-7} arylene, C_{5-7} cyclic alkylene and C_{3-7} heterocyclylene, which may be optionally substituted;

at least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}$, and R^{16} is selected from L-A, where L is a single bond or a C_{1-7} alkylene group and A is an ammonium group paired with a counterion selected from Cl, Br and I;

and/or one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}$, and R^{16} is L-A', where L is as defined above and A' is a ammonium linking group bound to a solid support and paired with a counterion selected from Cl, Br and I.

The preferences expressed above also apply to the catalysts of formula Ib, where appropriate.

The reaction may be carried out under solvent-free conditions, depending on the epoxides used. In some cases, the epoxides or the cyclic carbonates may act as a solvent for the catalyst. In particular, the disclosed embodiments show that propylene carbonate acts a suitable reaction solvent.

Some reactions may need the addition of a co-catalyst, Y^- , and in particular MY, where M is a suitable cation, such as onium halides, which include, but are not limited to, R_4NY , R_3SY , R_4PY and R_4SbY , where each R is independently selected from optionally substituted C_{1-10} alkyl, C_{3-20} heterocyclyl and C_{5-20} aryl groups and one R can be an acyl group, and simple halides, e.g. NaCl, KI.

It is preferred that the co-catalyst for this reaction is of the form R_4NY , where each R is independently C_{1-10} alkyl and Y is selected from I, Br and Cl. R is preferably selected from C_{3-5} alkyl, and more preferably is butyl. Y is preferably Br. Therefore, a particularly preferred co-catalyst is Bu_4NBr (TBAB). The amount of co-catalyst is preferably less than

18

2.5%, more preferably less than 1.0 mol % and most preferably less than 0.5 mol %. In some embodiments, no separate co-catalyst is present.

Manufacture of Dimeric Aluminium(Salen) Complexes

In a third aspect of a disclosed embodiment, there is provided a process for the production of dimeric aluminium (salen) catalysts of formula I.

When the catalyst of formula I comprises one or more ammonium group paired with a counterion, it may be synthesised from a precursor comprising the corresponding ammonia groups by reaction with an organic halide (i.e. a C_{1-7} alkyl, C_{3-20} heterocyclyl or C_{5-20} aryl halide), or an organic group with another leaving group (e.g. tosylate).

When the catalyst of formula I comprises an ammonium linking group bound to a solid support, it may be synthesised from a precursor catalyst comprising a corresponding ammonia group by reaction with a halide derived solid support or a solid support derivatized with another leaving group (e.g. tosylate).

EXAMPLES

General Experimental Methods

IR spectroscopy

IR spectra of liquids or of solids dissolved in a solvent were recorded between NaCl plates on a PE Spectrum 1 spectrometer. IR spectra of pure solids were recorded on a Nicolet380 FTIR spectrometer fitted with a 'Smart orbit' attachment.

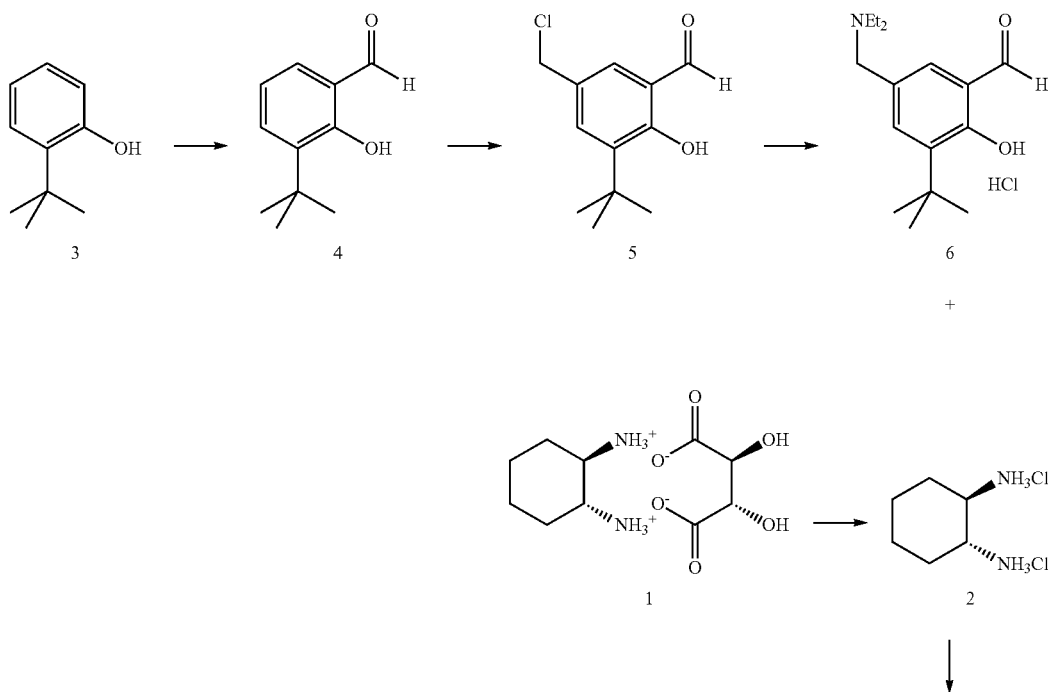
NMR

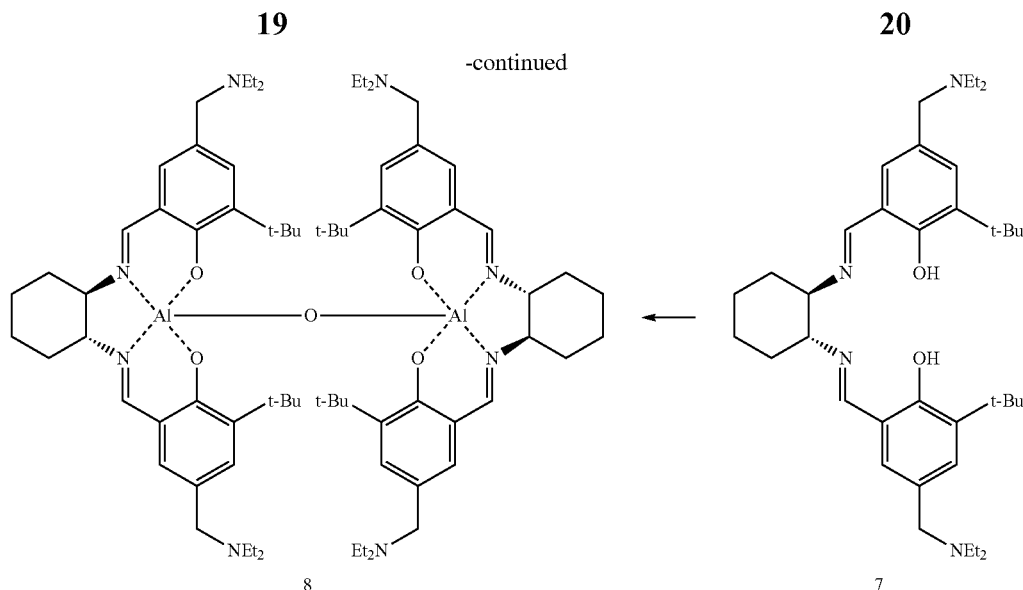
All NMR spectra were recorded at ambient temperature on a Bruker Avance 300 spectrometer. The sample was dissolved in $CDCl_3$ unless specified otherwise.

Mass Spectroscopy

Low resolution EI and CI spectra were recorded on a Varian Saturn 2200 GC-mass spectrometer. Low and high resolution electrospray spectra (ESI) were recorded on a Waters LCT Premier mass spectrometer.

Synthesis of Key Intermediates





(a) (1R,2R)-Cyclohexane-1,2-diammonium dichloride (2)

(Larrow, J. F. et al., *J. Org. Chem.* 1994, 59, 193)

To a suspension of (1R,2R)-cyclohexane-1,2-diammonium L-tartrate (1) (13.7 g, 52 mmol) in MeOH (50 mL) was added a cooled solution (0° C.) of acetyl chloride (27.4 mL, 385 mmol) in MeOH (50 mL). The solution was stirred at room temperature overnight. The resulting precipitate was filtered off, washed with Et₂O (10 mL) and dried by suction to leave the desired product as a white powder. A second crop was obtained by diluting the mother liquor with Et₂O (200 mL) and cooling for half an hour. The product was collected and dried to yield a white powder. Yield: 80%. Crystalline white powder. $[\alpha]_D^{20}$ -16 (c 5.0, aq. 1M HCl). ¹H-NMR δ_H (DMSO-d₆): 1.05-1.25 (2H, m, CH₂CH₂CHN), 1.30-1.55 (2H, m, CH₂CH₂CHN), 1.60-1.75 (2H, m, CH₂CHN), 2.00-2.15 (2H, m, CH₂CHN), 3.13-3.30 (2H, m, CHN), 8.70 (6H, br s, NH₃).

(b) 3-tert-Butylsalicylaldehyde (4)

(Gisch, N.; Balzarini, J.; Meier, C. *J. Med. Chem.* 2007, 50, 1658)

To a stirred suspension of 2-tert-butylphenol (3) (4.55 g, 30 mmol), magnesium chloride (5.71 g, 60 mmol) and paraformaldehyde (2.08 g, 66 mmol) in THF (120 mL) at room temperature, was added triethylamine (8.35 mL, 60 mmol) dropwise. The reaction was heated to reflux for 3 hours to give an orange suspension. This was extracted using EtOAc (3×50 mL). A small amount of diluted HCl can be added if a permanent emulsion is formed. The organic layers were dried over MgSO₄ and the volatiles evaporated under low pressure to yield a pale yellow oil which did not need any further purification. It can become dark green on storage. Yield: 90%. Pale yellow oil. ¹H-NMR δ_H : 1.44 (9H, s, 3×CH₃), 6.97 (1H, t, J=7.5 Hz, H_{Ar}), 7.41 (1H, dd, J=1.5 Hz, J=7.5 Hz, H_{Ar}), 7.54 (1H, dd, J=1.2 Hz, J=7.5 Hz, H_{Ar}), 9.88 (1H, s, CHO), 11.82 (1H, s, OH).

(c) 3-tert-Butyl-5-chloromethylsalicylaldehyde (5)

A mixture of 3-tert-butylsalicylaldehyde (4) (3.56 g, 20 mmol) and paraformaldehyde (1.20 g, 40 mmol) was stirred with concentrated HCl (15 mL) for 14 days, although with the first drops of concentrated HCl, the emulsion became red. The mixture was then neutralized by treatment with a saturated solution of Na₂CO₃. The mixture was extracted with EtOAc (3×30 mL). Organic layers were dried over MgSO₄ and the volatiles were evaporated under low pressure to give a beige solid which did not require further purification. Yield: 97%. Beige to red solid. ¹H-NMR δ_H : 1.43 (9H, s, 3×CH₃), 4.59 (2H, s, CH₂), 7.43 (1H, d, J=2.1 Hz, H_{Ar}), 7.52 (1H, d, J=2.1 Hz, H_{Ar}), 9.87 (1H, s, CHO), 11.86 (1H, s, OH).

(d) 3-tert-Butyl-5-diethylaminomethylsalicylaldehyde hydrochloride (6)

To a solution of 3-tert-butyl-5-chloromethylsalicylaldehyde (5) (226.5 mg, 1 mmol) in acetonitrile (60 mL), diethylamine (1 mmol) was added dropwise to give a greenish solution. The reaction was stirred at 30° C. overnight. After evaporation of volatiles, a green oil was obtained which was used without any purification for the next step. Yield: 77%. Green oil. \square_{max} 3300, 2899 and 1720 cm⁻¹. ¹H-NMR δ_H : 1.35 (9H, s, C(CH₃)₃), 1.45 (6H, t, J=7.2 Hz, 2×CH₂CH₃), 3.43 (4H, q, J=7.2 Hz, 2×CH₂CH₃), 4.90 (2H, s, CCH₂N), 7.57 (1H, d, J=2.1 Hz, H_{Ar}), 8.03 (1H, d, J=2.1 Hz, H_{Ar}), 9.98 (1H, s, CHO), 12.00 (1H, br s, OH). ¹³C-NMR δ_C (CDCl₃, 75 MHz): 10.8, 28.3, 33.7, 45.8, 56.0, 119.5, 129.8, 130.3, 133.7, 137.0, 159.0, 195.9.

HRMS: Calcd. for C₁₆H₂₆NO₂⁺ 264.1964. Found 264.1953.

(e) (1R,2R)-N,N'-Bis(3-tert-butyl-5-diethylaminomethylsalicylidene)cyclohexane-1,2-diamine (7)

(1R,2R)-cyclohexane-1,2-diammonium dichloride (2) (93.5 mg, 0.5 mmol) and NaOMe (55 mg, 1 mmol) were stirred in MeOH (10 mL) for 30 min. Then, a solution of

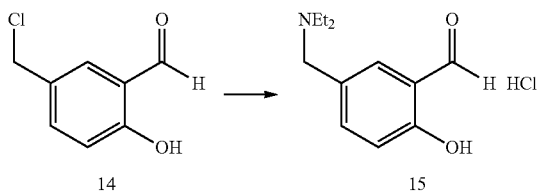
21

3-tert-butyl-5-diethylaminomethylsalicylaldehyde hydrochloride (6) (299.8 mg, 1 mmol) in MeOH (5 mL) was added and the solution, which became rapidly yellow, was stirred overnight at 30° C. Evaporation of MeOH was followed by addition of a saturated solution of Na₂CO₃ (20 mL). Organic compounds were extracted using dichloromethane (3×15 mL). It is important that the aqueous phase remains completely colourless and that the organic layer changes colour from orange to green. Organic layers were dried over MgSO₄ and volatiles were removed under vacuum to give a greenish slurry oil which was used without any purification in the next step.

Yield: 55%. Yellow-green oil. $[\alpha]_D^{20}$ -184.5 (c 1.0, CHCl₃). \square_{max} 3410, 2899, 1610, 1550 and 830 cm⁻¹. ¹H-NMR δ_H : 0.99 (12H, t, J=7.2 Hz, 4×CH₂CH₃), 1.40 (18H, s, 2×C(CH₃)₃), 1.50-2.05 (8H, m, (CH₂)₄), 2.44 (8H, q, J=7.2 Hz, 4×CH₂CH₃), 3.40-3.50 (6H, m, 2×CHN, 2×CCH₂N), 6.95 (2H, d, J=1.8 Hz, 2×H_{Ar}), 7.17 (2H, d, J=1.8 Hz, 2×H_{Ar}), 8.28 (2H, s, 2×HC=N), 13.77 (2H, br s, 2×OH). ¹³C-NMR δ_C : 11.9, 24.4, 29.6, 33.2, 34.8, 46.8, 57.3, 72.5, 118.4, 128.8, 129.8, 130.1, 136.9, 159.3, 165.7. HRMS (ESI): Calcd. for C₃₈H₆₁N₄O₂⁺ 605.4795. found 605.4783.

(f) Bis[(1R,2R)—N,N'-Bis(3-tert-butyl-5-diethylaminomethylsalicylidene)cyclohexane-1,2-diaminoaluminium(III)]oxide (8)

This reaction has to be performed under an inert atmosphere in dry conditions. Ligand (7) (1 mmol) and Al(OEt)₃ (324.1 mg, 2 mmol) were dissolved in toluene (10 mL). The reacting mixture was heated to reflux for 5 hours. An occasional residue of alumina could be removed by filtering through a sinter. The mother liquor was evaporated and then, H₂O (30 mL) and dichloromethane (30 mL) were added. The complex was extracted using dichloromethane (3×20 mL) and organic layers were dried over MgSO₄. Volatiles were removed under low pressure to give a pale solid, which was recrystallised using acetonitrile. Yield: 40%. Pale green solid. $[\alpha]_D^{20}$ -522 (c 1.0, CHCl₃). \square_{max} 2865, 1626, 1548, 1440, 1027, 836 and 577 cm⁻¹. ¹H-NMR δ_H : 1.02 (24H, t, J=7.2 Hz, 8×CH₂CH₃), 1.46 (36H, s, 4×C(CH₃)₃), 1.50-2.15 (16H, m, 2×(CH₂)₄), 2.52-2.7 (16H, m, 8×CH₂CH₃), 3.10-3.15 (2H, m, 2×CHN), 3.50-3.60 (8H, m, 4×CCH₂N), 3.80-3.85 (2H, m, 2×CHN), 7.09 (4H, d, J=5.7 Hz, 4×H_{Ar}), 7.35 (4H, d, J=5.7 Hz, 4×H_{Ar}), 8.19 (2H, s, 2×HC=N), 8.37 (2H, s, 2×1-CN). ¹³C-NMR δ_C : 10.2, 24.7, 29.9, 30.1, 35.0, 47.1, 57.6, 73.2, 118.9, 119.2, 128.9, 135.3, 141.7, 157.2, 165.1. m/z (ESI) 661.5 (100), 1275.9 (80), 1276.9 (72), 1277.9 (32), 1278.9 (16), 1279.9 (4)

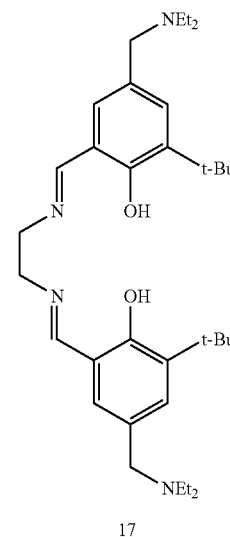
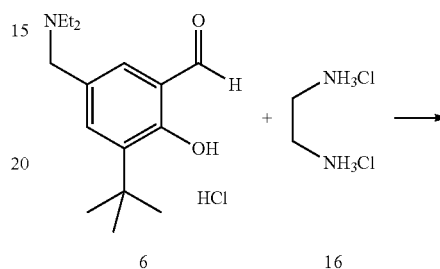


(g) 5-Diethylaminomethylsalicylaldehyde 15

To a solution of 5-(chloromethyl)salicylaldehyde (14) (345 mg, 2 mmol) in acetonitrile (70 mL), diethylamine (0.21 mL,

22

2 mmol) was added and the mixture refluxed overnight. Then, the solvent was evaporated to give compound 15 (625 mg, 99%) as a yellow oil. \square_{max} 3383, 2648 and 1653 cm⁻¹. ¹H-NMR δ_H 1.37 (6H, t, J=7.2 Hz, 2×CH₂CH₃), 3.43 (4H, q, J=7.2 Hz, 2×CH₂CH₃), 4.09 (2H, s, CCH₂N), 7.05 (1H, d, J=8.6 Hz, H_{Ar}), 8.03 (1H, d, J=8.6 Hz, H_{Ar}), 8.14 (1H, s, H_{Ar}), 9.98 (1H, s, CHO), 12.32 (1H, br s, OH). ¹³C-NMR δ_C 11.4, 46.4, 56.0, 118.8, 121.3, 136.7, 139.0, 162.7, 196.5. m/z (ESI) 208 (MH⁺, 100), 293 (30), 317 (10). HRMS (ESI): Calculated for M⁺ (C₁₂H₁₇NO₂⁺) 208.1338. Found 208.1355.



(h) N,N'-Bis(3-tert-butyl-5-diethylaminomethylsalicylidene)ethane-1,2-diamine 17

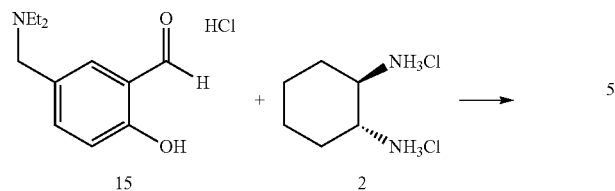
Compound 17 was synthesised from compounds 6 and 16 in an analogous manner to step (e) above. A yellow oil was obtained in 56% yield. \square_{max} 2965, 2524 and 1629 cm⁻¹. ¹H-NMR δ_H 1.44 (12H, t J=7.5 Hz, 4×CH₂CH₃), 1.51 (18H, s, 2×C(CH₃)₃), 2.70-2.80 (4H, m, CCH₂N), 3.02 (8H, q J=7.2 Hz, 4×CH₂CH₃), 3.60-3.80 (4H, m, 2×CH₂), 7.07-7.35 (4H, m, 4×H_{Ar}), 8.25 (2H, s, 2×HC=N), 13.99 (2H, br s, 2×OH). ¹³C-NMR δ_C 10.4, 28.0, 33.3, 45.2, 55.7, 58.1, 116.8, 128.2, 128.8, 135.6, 157.7, 165.3, 165.8. m/z (ESI) 551 (MH⁺, 100), 524 (30).

HRMS (ESI): Calculated for MH⁺ (C₃₄H₅₅N₄O₂⁺) 551.4325. Found 551.4294.

23

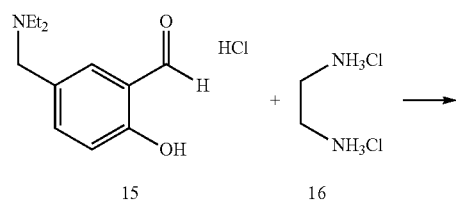
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-continued



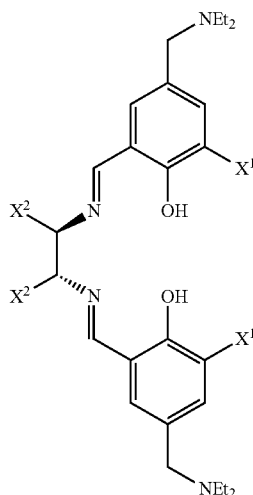
(i) (1R,2R)—N,N'-Bis(5-diethylaminomethylsalicylidene)cyclohexane-1,2-diamine 18

Compound 18 was synthesised from compounds 15 and 2 in an analogous manner to step (e) above. A yellow oil was obtained in 65% yield. $[\alpha]_D^{20}$ -302 (c 0.1, CHCl_3). \square_{max} 2939, 1631 and 1089 cm^{-1} . $^1\text{H-NMR}$ δ_H 1.25 (12H, t J=7.2 Hz, $4 \times \text{CH}_2\text{CH}_3$), 1.50-2.00 (8H, m, $(\text{CH}_2)_4$) 2.89 (8H, q J=7.6 Hz, $4 \times \text{CH}_2\text{CH}_3$), 2.90-3.00 (4H, m, $2 \times \text{CCH}_2\text{N}$), 3.90-4.00 (2H, m, $2 \times \text{CH}$), 6.83 (2H, d J=8.3 Hz, $2 \times \text{H}_{Ar}$), 7.36 (2H, d J=8.4 Hz, $2 \times \text{H}_{Ar}$), 7.43 (2H, s, $2 \times \text{H}_{Ar}$) 8.25 (2H, s, $2 \times \text{HC}=\text{N}$), 13.40 (2H, br s, $2 \times \text{OH}$). $^{13}\text{C-NMR}$ δ_C 9.5, 24.4, 33.0, 46.9, 56.0, 72.6, 117.7, 118.9, 120.8, 134.3, 134.8, 161.4, 165.3. m/z(ESI) 493 (MH^+ , 100), 420 (20). HRMS (ESI): Calculated for MH^+ ($\text{C}_{30}\text{H}_{45}\text{N}_4\text{O}_2^+$) 493.3542. Found 493.3544.

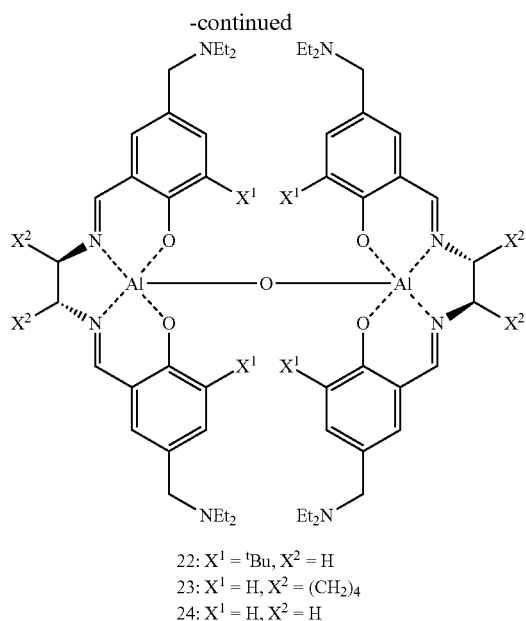


(j) N,N'-Bis(5-diethylaminomethylsalicylidene)ethane-1,2-diamine 19

Compound 19 was synthesised from compounds 15 and 16 in an analogous manner to step (e) above. A yellow oil was obtained in 53% yield. \square_{max} 2801, 1632, and 1083 cm^{-1} . $^1\text{H-NMR}$ δ_H 1.21 (12H, t J=7.5 Hz, $4 \times \text{CH}_2\text{CH}_3$), 2.70-2.80 (4H, m, CCH_2N), 2.96 (8H, q J=7.2 Hz, $4 \times \text{CH}_2\text{CH}_3$), 3.85-3.95 (4H, m, $2 \times \text{CH}_2$), 6.83 (2H, d J=8.6 Hz, $2 \times \text{H}_{Ar}$), 7.26 (2H, d J=8.6 Hz, $2 \times \text{H}_{Ar}$), 7.42 (2H, s, $2 \times \text{H}_{Ar}$), 8.34 (2H, s, $2 \times \text{HC}=\text{N}$), 13.21 (2H, br s, $2 \times \text{OH}$). $^{13}\text{C-NMR}$ δ_C 11.9, 43.5, 47.8, 57.2, 117.0, 129.6, 126.5, 130.4, 132.0, 133.4, 166.9. m/z(ESI) 439 (MH^+ , 100), 420 (20). HRMS (ESI): Calculated for MH^+ ($\text{C}_{34}\text{H}_{55}\text{N}_4\text{O}_2^+$) 439.3073. Found 439.3090.



17: $\text{X}^1 = t\text{Bu}$, $\text{X}^2 = \text{H}$
 18: $\text{X}^1 = \text{H}$, $\text{X}^2 = (\text{CH}_2)_4$
 19: $\text{X}^1 = \text{H}$, $\text{X}^2 = \text{H}$

25

(k) Bis[N,N'-Bis(3-tert-butyl-5-diethylaminomethyl-salicylidene)ethane-1,2-diaminoaluminum(III)]oxide 22, Bis[(1R,2R)—N,N'-Bis(5-diethylaminomethylsalicylidene)-cyclohexane-1,2-diaminoaluminum(III)]oxide 23 and Bis[N,N'-Bis(5-diethylaminomethylsalicylidene)ethane-1,2-diaminoaluminum(III)]oxide 24

Ligands 17-19 were converted to complexes 22-24 in an analogous manner to step (f) above.

22: pale yellow solid obtained in 55% yield. \square_{\max} 2522 and 2159 cm^{-1} . $^1\text{H-NMR}$ δ_{H} 1.10-1.20 (24H, m, 8 \times CH₂CH₃), 1.43 (36H, s, 4 \times C(CH₃)₃), 2.90-3.15 (16H, m, 8 \times CH₂CH₃), 3.50-3.60 (8H, m, 4 \times CCH₂N), 3.70-4.00 (8H, m, 4 \times CH₂N), 7.19 (4H, s, 4 \times H_{Ar}), 7.30 (4H, s, 4 \times H_{Ar}), 8.33 (4H, s, 4 \times HC=N). $^{13}\text{C-NMR}$ δ_{C} 11.2, 24.2, 33.6, 46.5, 55.3, 55.9, 120.9, 135.5, 137.5, 137.8, 139.6, 140.9, 162.0. m/z (ESI) 1170 (10), 1169 (35), 1168 (90), 1167 (MH⁺, 100).

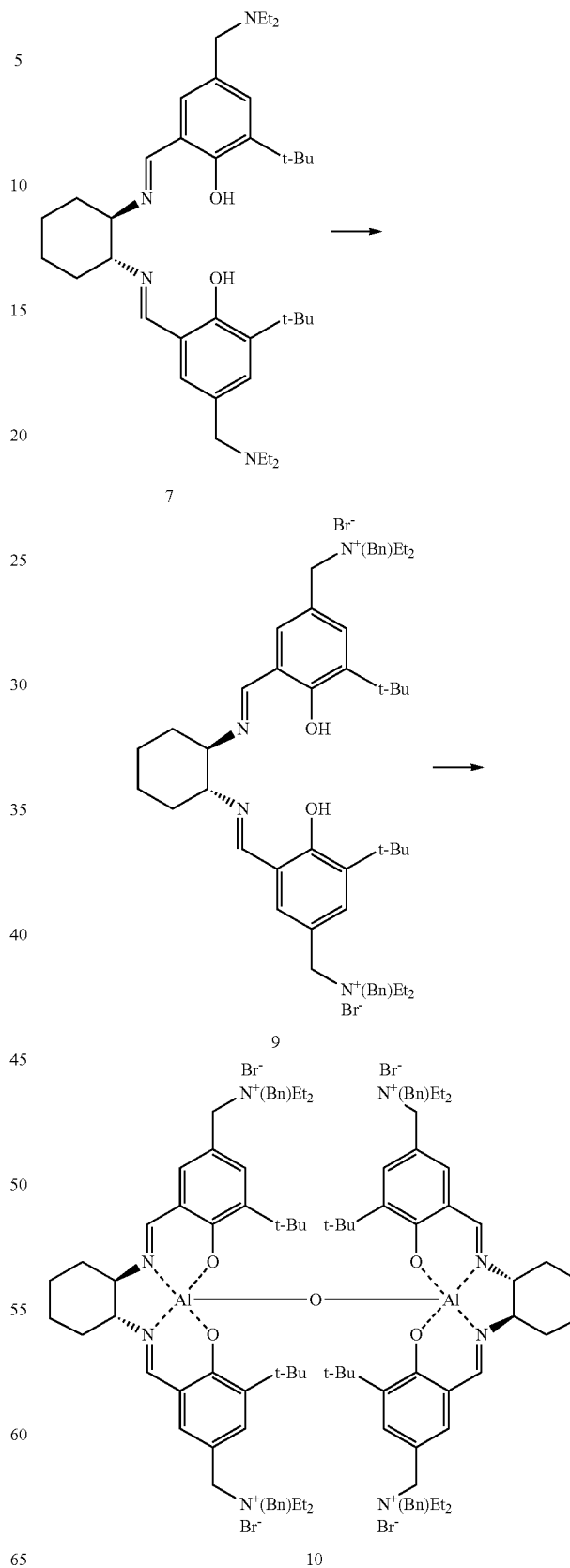
HRMS (ESI): Calculated for MH⁺ (C₆₈H₁₀₄N₈O₅Al₂⁺) 1167.7839. Found 1167.7799.

23: pale yellow solid obtained in 67% yield. \square [a]_D²⁰ -170 (c 0.01, DMSO). \square_{\max} 2859, 1631 and 1084 cm^{-1} . $^1\text{H-NMR}$ δ_{H} (DMSO-d₆): 1.04-1.99 (24H, m, 8 \times CH₂CH₃), 1.50-2.15 (16H, m, 2 \times (CH₂)₄), 2.5-2.6 (16H, m, 8 \times CH₂CH₃), 3.1-4.5 (12H, m, 4 \times CHN+4 \times CCH₂N), 6.91 (4H, d, J=7.6 Hz, 4 \times H_{Ar}), 7.40 (4H, d J=7.6 Hz, 4 \times H_{Ar}), 7.55 (4H, s, 4 \times H_{Ar}), 8.43 (4H, s, 4 \times HC=N).

24: pale yellow solid obtained in 65% yield. \square_{\max} 2971, 2225 and 1634 cm^{-1} . $^1\text{H-NMR}$ δ_{H} (DMSO-d₆): 1.05 (24H, m, 8 \times CH₂CH₃), 2.15-3.5 (24H, m, 8 \times CH₂CH₃+4 \times CCH₂N), 3.90 (8H, m, CH₂N), 6.81 (4H, d J=5.7 Hz, 4 \times H_{Ar}), 7.32 (8H, m, 8 \times H_{Ar}), 8.50 (4H, s, HC=N).

26

Example 1



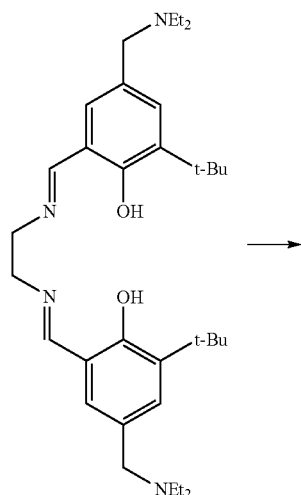
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(a) (1R,2R)—N,N'-Bis[3-tert-butyl-5-(N-benzyl-N,N-diethylaminomethyl)salicylidene]cyclohexane-1,2-diamine dibromide (9)

To a solution of (1R,2R)—N,N'-bis(3-tert-butyl-5-diethylaminomethylsalicylidene)-cyclohexane-1,2-diamine (7) (604.9 mg, 1 mmol) in acetonitrile (60 mL), benzyl bromide (342.1 mg, 2 mmol) was added dropwise to give a yellow solution. The reaction was stirred at 30° C. overnight. After evaporation of volatiles, a yellow oil was obtained which was recrystallised from n-hexane. Yield: 55%. Bright yellow solid. $[\alpha]_D^{20}$ -38.6 (c 1.0, CHCl₃). \square_{max} 3392, 2960, 1608, 1545 and 1470 cm⁻¹. ¹H-NMR δ_H : 1.00-2.00 (38H, m, 10×CH₃, (CH₂)₄), 3.40-3.50 (2H, m, 2×CHN), 3.56 (8H, q, J=7.5 Hz, 4×CH₂CH₃), 4.20 (4H, 2×CCH₂N), 4.99 (4H, 2×CCH₂N), 6.44 (2H, d, J=2.4 Hz, 2×H_{Ar}), 7.65 (2H, d, J=2.4 Hz, 2×H_{Ar}), 8.38 (2H, s, 2×HC=N), 14.30 (2H, br s, 2×OH). ¹³C-NMR δ_C : 11.3, 23.4, 29.3, 31.2, 35.1, 51.1, 60.3, 60.4, 72.7, 120.2, 128.6, 128.8, 129.2, 129.9, 130.6, 134.9, 157.2, 163.9.

(b) Bis[(1R,2R)—N,N'-Bis(3-tert-butyl-5-(N-benzyl-N,N-diethylaminomethyl)salicylidene bromide)]cyclohexane-1,2-diaminoaluminium(III) oxide (10)

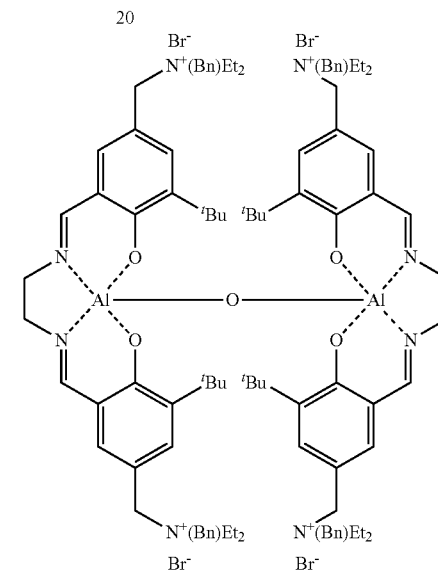
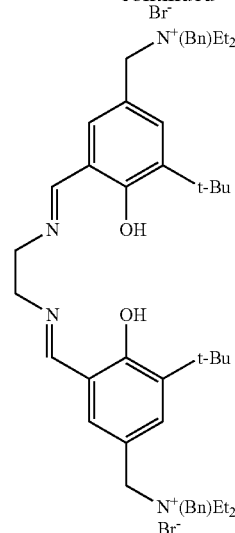
This reaction has to be performed under an inert atmosphere in dry conditions. Ligand (9) (1 mmol) and Al(OEt)₃ (324.1 mg, 2 mmol) were dissolved in a mixture of toluene (5 mL) and ethanol (5 mL). The reacting mixture was heated to reflux for 5 hours. An occasional residue of alumina could be removed by filtering through a sinter. The mother liquor was evaporated, then H₂O (30 mL) and dichloromethane (30 mL) were added. The complex was extracted using dichloromethane (3×20 mL) and organic layers were dried over MgSO₄. Volatiles were removed under low pressure to give a pale solid, which was recrystallised using Et₂O. Yield: 33%. Pale yellow solid. $[\alpha]_D^{20}$ -281 (c 1.0, CHCl₃). IR 2946, 1624, 1551, 1470, 1208 and 1030 cm⁻¹. ¹H-NMR δ_H : 1.05 (24H, t, J=7.3 Hz, 8×CH₂CH₃), 1.45 (36H, s, 4×C(CH₃)₃), 1.50-2.20 (16H, m, 2×(CH₂)₄), 2.45-2.50 (16H, m, 8×CH₂CH₃), 3.10-3.15 (2H, m, 2×CHN), 3.40-3.50 (16H, m, 8×CCH₂N), 3.80-3.85 (2H, m, 2×CHN), 7.10-7.50 (28H, m, 28×H_{Ar}), 8.20 (2H, s, 2×HC=N), 8.35 (2H, s, 2×HC=N). ¹³C-NMR δ_C : 10.3, 24.5, 30.0, 30.2, 34.6, 48.3, 57.6, 60.2, 73.8, 119.1, 119.6, 124.6, 127.4, 127.9, 128.9, 135.2, 141.6, 156.5, 166.1.



17

28

-continued



21

(c) N,N'-Bis[3-tert-butyl-5-(N-benzyl-N,N-diethylaminomethyl)salicylidene]ethane-1,2-diamine dibromide (20)

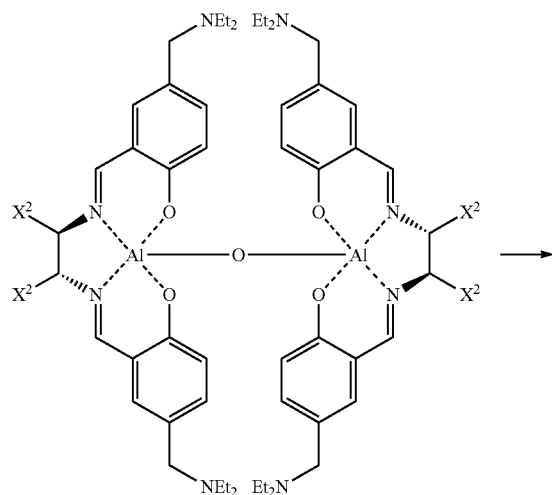
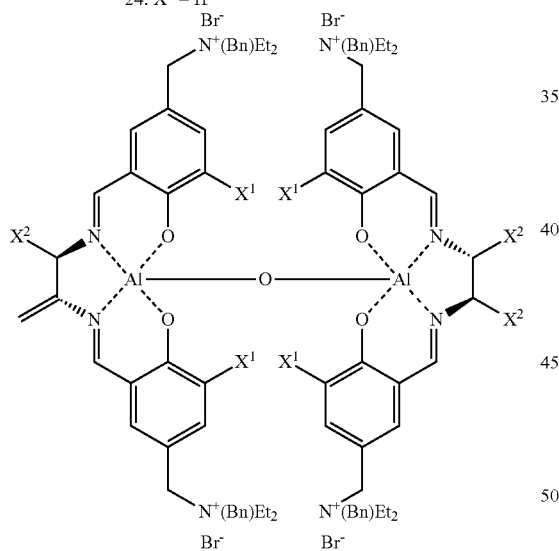
The bis-ammonium salt (20) was synthesised from the salen ligand (17) in an analogous manner to step (a) above. \square_{max} 3383, 2648 and 1647 cm⁻¹. ¹H-NMR δ_H 1.44 (12H, t, J=7.5 Hz, 4×CH₂CH₃), 1.51 (18H, s, 2×C(CH₃)₃), 2.78 (8H, q, J=7.2 Hz, 4×CH₂CH₃), 3.6-3.8 (4H, m, 2×CH₂N), 3.9-4.1 (4H, m, CCH₂N), 7.0-7.4 (4H, m, 4×H_{Ar}), 8.25 (2H, s, 2×HC=N), 13.99 (2H, br s, 2×OH). ¹³C-NMR δ_C 10.9, 29.6, 35.1, 46.5, 56.6, 59.7, 65.7, 118.8, 121.1, 127.5, 128.8, 129.0, 129.5, 135.5, 137.3, 139.6, 141.0, 162.6.

(d) Bis[N,N'-Bis(3-tert-butyl-5-(N-benzyl-N,N-diethylaminomethyl)salicylidene bromide)]ethane-1,2-diaminoaluminium(III) oxide (21)

The catalyst (21) was synthesised from the bis-ammonium salt (20) in an analogous manner to step (b) above. A pale

29

yellow solid was obtained in 42% yield. \square_{\max} 2950, 1634 and 1029 cm^{-1} . $^1\text{H-NMR } \delta_H$ 1.05 (24H, t $J=7.3\text{ Hz}$, $8\times\text{CH}_2\text{CH}_3$), 1.45 (36H, s, $4\times\text{C}(\text{CH}_3)_3$), 2.95-3.15 (16H, m, $8\times\text{CH}_2\text{CH}_3$), 3.20-3.45 (4H, m, $2\times\text{CH}_2\text{N}$), 3.90-4.30 (4H, m, $2\times\text{CH}_2\text{N}$), 4.50 (8H, s, $4\times\text{CCH}_2\text{N}$), 7.10-7.50 (28H, m, $28\times\text{H}_{Ar}$), 8.00 (2H, s, $2\times\text{HC}=\text{N}$), 8.13 (2H, s, $2\times\text{HC}=\text{N}$). $^{13}\text{C-NMR } \delta_C$ 11.5, 30.0, 35.7, 46.91, 55.4, 57.3, 65.7, 119.2, 119.6, 126.3, 131.1, 132.5, 132.6, 134.4, 141.9, 164.9, 170.1.

23: $\text{X}^2 = (\text{CH}_2)_4$ 24: $\text{X}^2 = \text{H}$ 25: $\text{X}^2 = (\text{CH}_2)_4$ 26: $\text{X}^2 = \text{H}$

(e) Bis[(1R,2R)—N,N'-Bis(5-(N-benzyl-N,N-diethylaminomethyl)salicylidene) bromide]cyclohexane-1,2-diaminoaluminum(III) oxide (25) and Bis[N,N'-Bis(5-(N-benzyl-N,N-diethylaminomethyl)salicylidene) bromide]ethane-1,2-diaminoaluminum(III) oxide (26)

Benzyl bromide (0.07 mL, 0.6 mmol) was added to a solution of bimetallic complex (23) or (24) (0.1 mmol) in propylene carbonate (10 mL) and the reaction stirred at 85°C .

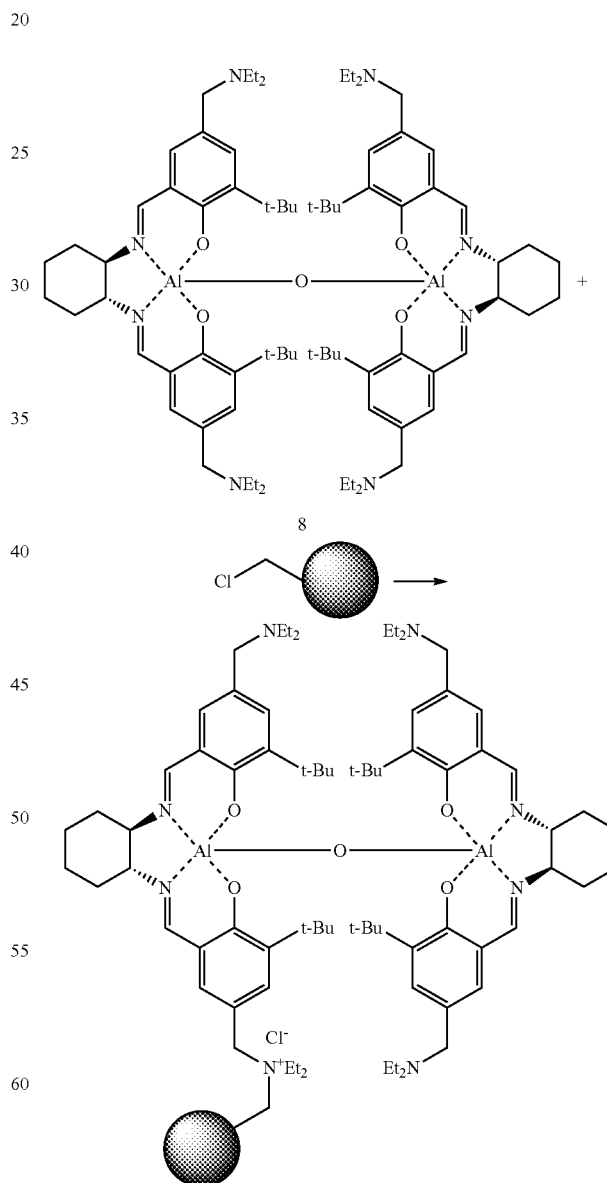
30

for 16 hours. The solvent was evaporated in vacuo to give compound (25) or (26) as a pale orange powder.

25: pale orange solid obtained in 52% yield. $[\alpha]_D^{20}$ -240 (c 0.01, DMSO). \square_{\max} 2923, 1625 and 1088 cm^{-1} . $^1\text{H-NMR } \delta_H$ (DMSO- d_6): 1.04-1.99 (24H, m, $8\times\text{CH}_2\text{CH}_3$), 1.50-2.15 (16H, m, $2\times(\text{CH}_2)_4$), 2.5-2.6 (16H, m, $8\times\text{CH}_2\text{CH}_3$), 3.1-3.9 (12H, m, $4\times\text{CHN}+4\times\text{CCH}_2\text{N}$), 4.50 (8H, s, $4\times\text{CCH}_2\text{N}$), 6.74 (4H, d, $J=7.3\text{ Hz}$, $4\times\text{H}_{Ar}$), 6.82 (4H, d, $J=7.3\text{ Hz}$, $4\times\text{H}_{Ar}$), 7.13-7.46 (24H, m, $24\times\text{H}_{Ar}$), 8.43 (4H, s, $4\times\text{HC}=\text{N}$).

26: pale orange solid obtained in 40% yield. \square_{\max} 2960, 1644 and 1032 cm^{-1} . $^1\text{H-NMR } \delta_H$ (DMSO- d_6): 0.99 (12H, m, $4\times\text{CH}_3\text{CH}_2$), 1.52 (12H, m, $4\times\text{CH}_3\text{CH}_2$), 3.21 (16H, q $J=7.1\text{ Hz}$, $8\times\text{CH}_2\text{CH}_3$), 4.1-4.3 (16H, m, $4\times\text{CCH}_2\text{N}+4\times\text{CH}_2\text{N}$), 4.57 (8H, s, $4\times\text{CCH}_2\text{N}$), 6.97 (4H, d, $J=8.3\text{ Hz}$, $4\times\text{H}_{Ar}$), 7.1-7.4 (24H, m, $24\times\text{H}_{Ar}$), 7.5-7.6 (4H, m, $4\times\text{H}_{Ar}$), 7.60 (4H, s, $4\times\text{HC}=\text{N}$).

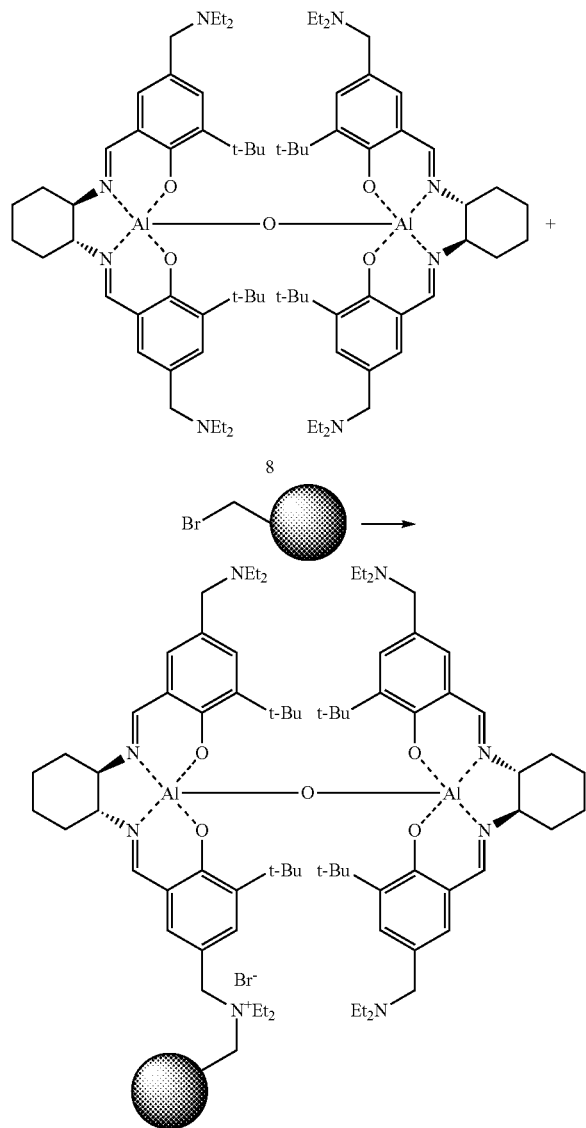
Example 2



31

Merrifield resin (120 mg, 0.2 mmol) was swollen in a minimal amount of DMF/dichloromethane. Complex (8) (240 mg, 0.4 mmol) was added and the mixture was stirred for 24 hours at 30° C. The resin was filtered off and washed using DMF (10 mL), DMF/dichloromethane (1:1) (10 mL), dichloromethane (10 mL), then it was dried under vacuum to give compound (12) as a yellow-coloured resin.

Example 3



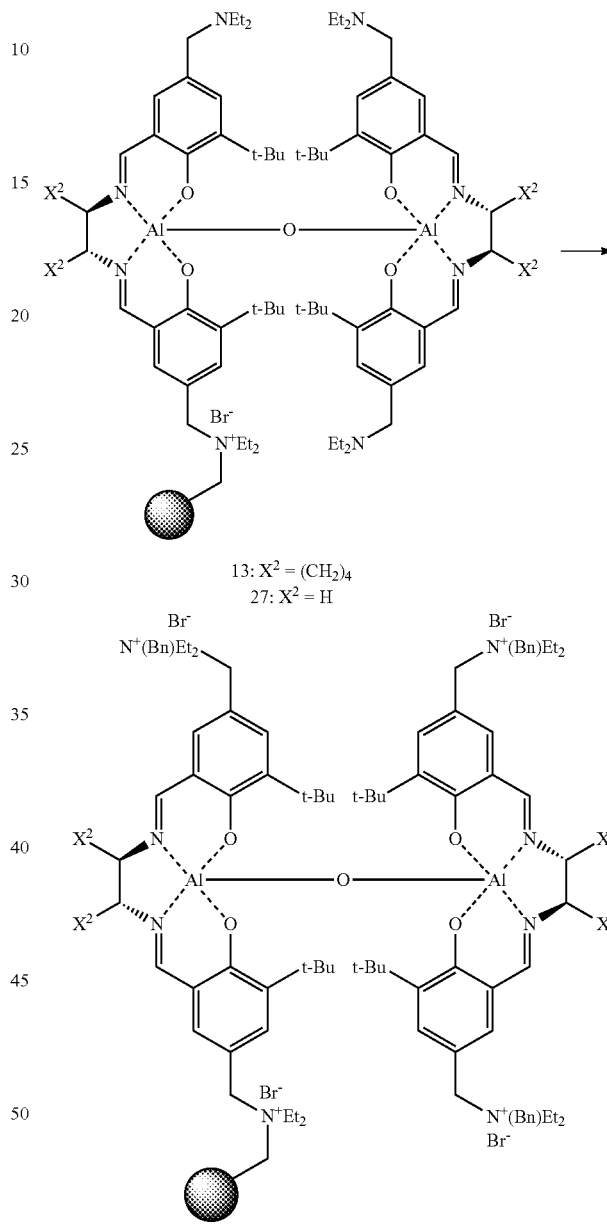
13

(a) Merrifield resin (120 mg, 0.2 mmol) was converted into the corresponding bromomethyl resin by treatment with a large excess of tetrabutylammonium bromide for several days in dichloromethane/DMF. Complex (8) (240 mg, 0.4 mmol) was added to this resin and the mixture was stirred for 24 hours at 30° C. The resin was filtered off and was washed using DMF (10 mL), DMF/dichloromethane (1:1) (10 mL), dichloromethane (10 mL), then dried under vacuum to give yellow-coloured resin (13). \square_{max} 2920, 2160, 1634, 1450 and 1066 cm^{-1} ,

32

(b) Immobilized catalyst 27 was synthesised from complex (22) in an analogous manner to step (a) above. 75% yield. \square_{max} 2963, 2159, 1634, 1451 and 1091 cm^{-1} .

Example 4

13: $\text{X}^2 = (\text{CH}_2)_4$ 27: $\text{X}^2 = \text{H}$

55

28: $\text{X}^2 = (\text{CH}_2)_4$ 29: $\text{X}^2 = \text{H}$

A sample of resin (13) or (27) (0.04 mmol) was swollen in DMF/ CH_2Cl_2 and a large excess of benzyl bromide (40 mg, 0.24 mmol) was added. The mixture was stirred at room temperature for 24 hours, then the reaction was filtered and the resin washed with DMF (10 mL), DMF/dichloromethane (1:1) (10 mL), dichloromethane (10 mL), then dried in vacuo to give a yellow-coloured resin.

(28): \square_{max} 2922, 2158, 1634, 1635, 1450 and 1028 cm^{-1} (29): 83% yield. \square_{max} 2961, 2153, 1636, 1544 and 1023 cm^{-1}

33

Example 5

a) Complexes (10), (21), (25) and (26)

Complexes (10), (21), (25) and (26) were tested in the reaction of some terminal epoxides with carbon dioxide at room temperature and atmospheric pressure.

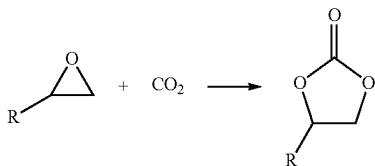


TABLE 1

Cyclic carbonate formation from epoxides.					
Entry	Complex	R	TBAB (mol-%)	Time (h)	Conversion (%) ^a
1	10	Ph	0	3	71
2	10	Ph	0	6	97
3	10	Ph	2.5	3	74
4	10	n-Bu	0	3	30 ^b
5	10	n-Bu	0	6	63 ^b
6	10	n-Octyl	0	3	44
7	10	n-Octyl	0	6	81
8	10	CH ₂ OH	0	3	55
9	10	CH ₂ OH	0	6	79
10	10	CH ₂ Cl	0	3	59 ^b
11	10	CH ₂ Cl	0	6	81 ^b
12 ^c	10	Me	0	3	50 ^b
13 ^c	10	Me	0	6	62 ^b
14	21	Ph	0	3	69
15	21	Ph	0	6	88
16	21	Ph	0	24	99
17	25	Ph	0	3	48
18	25	Ph	0	6	60
19	25	Ph	0	24	73
20	26	Ph	0	3	54
21	26	Ph	0	6	69
22	26	Ph	0	24	89

Reactions carried out neat with dimeric Al(salen) complex (2.5 mol-%) and the corresponding epoxide (1 mmol) under carbon dioxide at 26° C. and 1 atm unless otherwise stated.

^aDetermined by ¹H-NMR spectroscopy.

^bVolatile starting material was removed and the yield was determined by difference of weight.

^cReaction performed at 0° C.

b) Complexes 12 & 13

These complexes were used at 2.5 mol % in propylene carbonate (5 eq.) and styrene oxide (1 mmol) under carbon dioxide at 26° C. and 1 atmosphere pressure unless otherwise stated below. The reaction was carried out by dissolving the complexes (0.0415 mmol) in propylene carbonate (0.85 g) in a sample vial fitted with a magnetic stirrer bar. Styrene oxide (200 mg, 1.66 mmol) was then added and the sample vial was placed in a large conical flask. The conical flask was placed in an oil bath thermostatted at 26° C. Cardice pellets were added to the conical flask which was fitted with a rubber stopper pierced by a deflated balloon. The reaction was stirred for the required length of time, then filtered to remove the supported catalyst which was washed thoroughly with CH₂Cl₂ (20 mL). The filtrate and washings were combined and evaporated in vacuo and the residue analysed by ¹H NMR spectroscopy to determine the conversion of styrene oxide to styrene carbonate. The immobilized catalyst could be returned to the sample vial and reused, as shown with the repeated runs below.

34

Entry	Catalyst	Run	Time (h)	Conversion (%) ^a
1 ^{b,c}	12	1st	3	0
2 ^{b,c,d}	12	1st	3	17
3 ^{b,c,d}	12	2nd	3	9
4 ^c	12	1st	3	37
5 ^c	12	1st	6	67
6 ^c	12	1st	20	100
7 ^c	12	2nd	3	5
8 ^c	12	2nd	6	37
9 ^c	12	2nd	20	86
10 ^c	12	3rd	3	0
11 ^c	12	3rd	6	20
12 ^c	12	3rd	20	63
13	13	1st	3	11
14	13	1st	6	69
15	13	1st	20	100
16	13	2nd	3	0
17	13	2nd	6	37
18	13	2nd	20	94
19	13	3rd	3	5
20	13	3rd	6	25
21	13	3rd	20	70

^aDetermined by GC.

^bReaction performed solvent-free.

^cReaction performed in the presence of 2.5 mol % of TBAB.

^dOnly 0.5 mol % of the complex (12) was used.

The use of propylene carbonate as a solvent is compatible with the catalytic system.

c) Complexes (28) and (29)

Complexes (28) and (29) were tested at 2.5 mol % in the reaction of styrene oxide (1 mmol) with carbon dioxide at 26° C. and 1 atmosphere pressure in the presence of propylene carbonate (5 eq.) as a solvent, with 20 hours for each reaction. The complexes were found to be recyclable. The method is as in step b) above.

Complex (28) gave styrene carbonate yields of 79, 73, 66 and 60% over four consecutive reactions.

Complex (29) gave styrene carbonate yields of 79, 71, 67 and 64% over four consecutive reactions.

Example 6

(a) Synthesis of [Al(salen)]₂O Electrostatically Supported on Clays

Clays (0.5 g) were activated at 120° C. for three days prior to use. After the activation, the clay (0.5 g) was added to a solution of aluminium complex (21) (0.140 g, 0.08 mmol) in DMF (30 mL) and refluxed for 30 hours. Subsequently, the mixture was filtered and washed with DMF (4×20 mL), EtOAc (4×20 mL) and dichloromethane (3×20 mL) to yield a powder which was dried under vacuum for 24 hours.

[Al(salen)]₂O supported on Bentonite (30): Pale brown solid, yield 99%. □_{max} 3540, 2150, 1987 and 1659 cm⁻¹.

[Al(salen)]₂O supported on Montmorillonite K10 (31): Purple solid, yield 99%. □_{max} 3500, 1659 and 922 cm⁻¹.

[Al(salen)]₂O supported on Al pillared clay (32): Pale brown solid, yield 99%. □_{max} 3500, 1654 and 1034 cm⁻¹.

(b) Synthesis of Styrene Carbonate Using [Al(salen)]₂O Electrostatically Supported on Clays

Styrene oxide (0.2 g, 1.66 mmol) and catalyst (30-32) (0.5 g, 0.1 mmol/g support) in propylene carbonate (0.84 g) were placed in a sample vial fitted with a magnetic stirrer bar and placed in a large conical flask. The conical flask was placed in an oil bath thermostatted at 26° C. Cardice pellets were added to the conical flask which was fitted with a rubber stopper pierced by a deflated balloon. The contents of the reaction vial

35

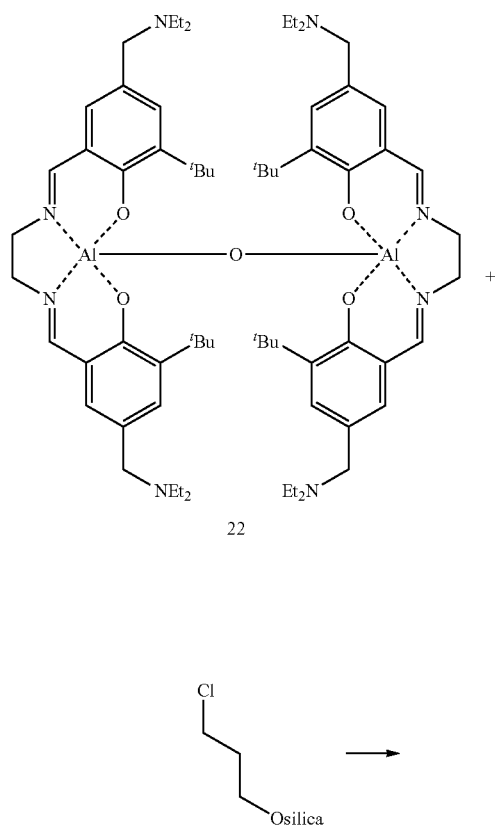
were stirred for 24 hours during which time the balloon inflated as the cardice pellets evaporated. The reaction was filtered to remove supported catalyst and the solution analysed by GC to determine the conversion of styrene oxide into styrene carbonate.

Catalyst	Conversion (%)
30	5%
31	3%
32	7%

Example 7

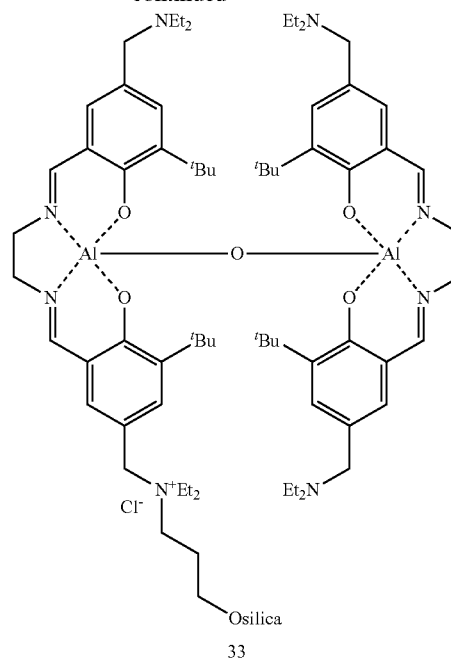
(a) Synthesis of Modified SiO₂

(3-Chloropropyl)-triethoxysilane (0.16 mL, 2 mmol) was added to a mixture of activated SiO₂ (2 g) in dry toluene (25 mL) and refluxed under N₂ for 24 hours. Subsequently, the mixture was filtered and washed with EtOAc (4×50 mL) to yield a yellow powder (95%). \square_{max} 2505, 2160 and 1975 cm⁻¹.

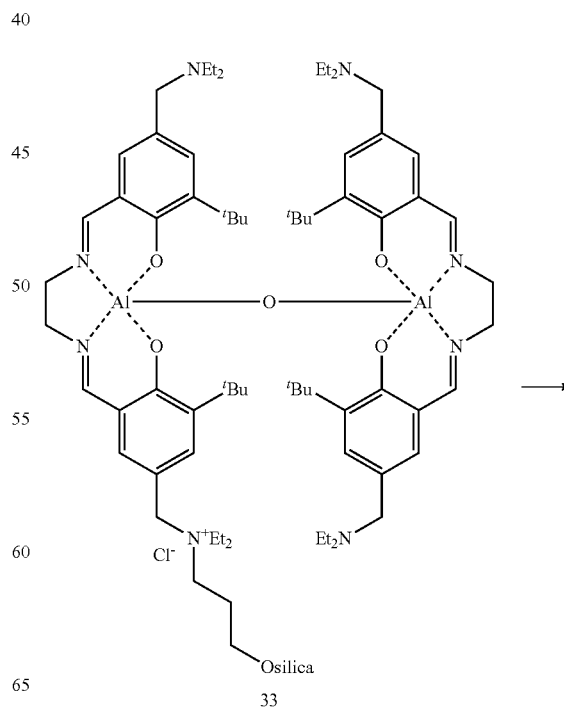
(b) Synthesis of [Al(salen)]₂O⁺Cl⁻ Supported on Modified SiO₂ (33)

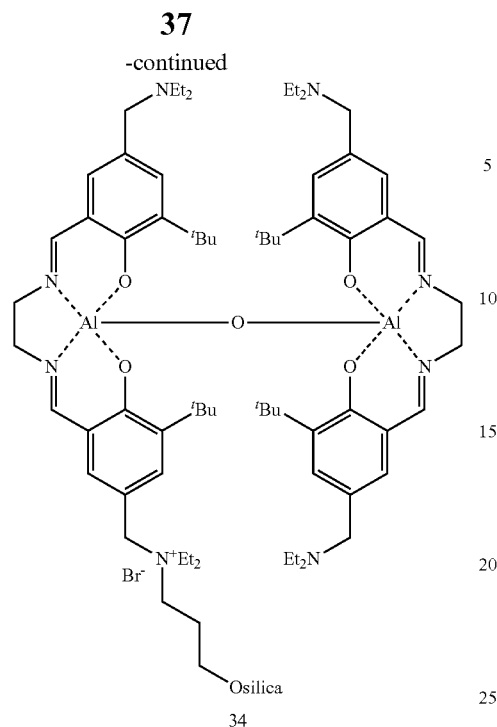
36

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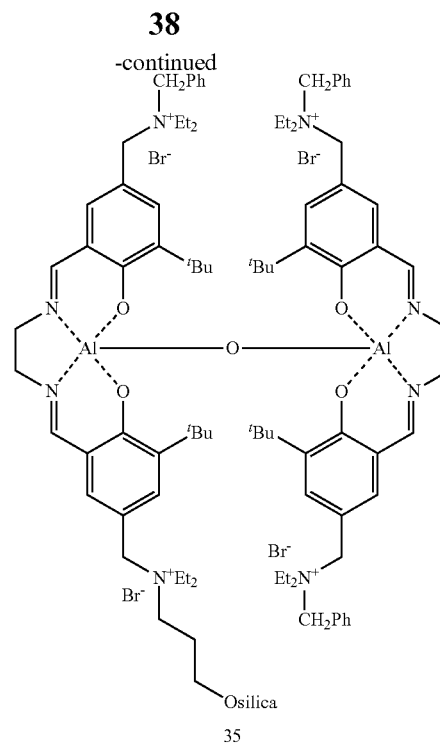
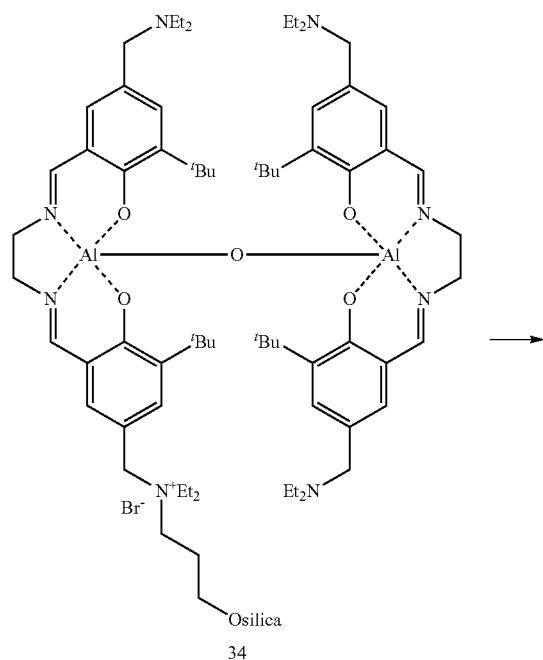
Modified SiO₂ (0.1 g) was added to a solution of aluminium complex (22) (0.175 g, 0.15 mmol) in CH₃CN (40 mL) and the mixture was refluxed overnight. Then, the mixture was filtered and washed with EtOAc (4×50 mL) to give silica supported complex (33) as a yellow powder. \square_{max} 3500, 1649 and 1070 cm⁻¹.

(c) Synthesis of [Al(salen)]₂O⁺Br⁻ Supported on Modified SiO₂ (34)



Tetrabutylammonium bromide (193 mg, 6 mmol) was added to a suspension of supported complex (33) (0.220 g, 1 mmol) in CH_3CN (40 mL) and the resulting mixture was refluxed overnight. Then, the mixture was filtered and washed with EtOAc (4×50 mL) to give silica supported complex (34) as a yellow powder. \square_{max} 3427, 1628 and 1070 cm^{-1} .

(d) Synthesis of Benzylated $[\text{Al}(\text{salen})]_2\text{O}^+\text{Br}^-$ Supported on Modified SiO_2 (35)



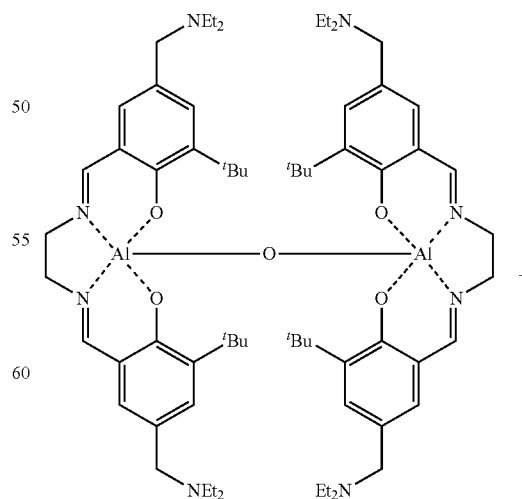
Benzyl bromide (0.09 mL, 0.72 mmol) was added to a suspension of supported catalyst (34) (0.240 g, 1 mmol) in CH_3CN (40 mL) and the resulting mixture was refluxed overnight. Subsequently, the mixture was filtered and washed with EtOAc (4×50 mL) to give silica supported complex (35) as a yellow powder. \square_{max} 3410, 1633 and 1078 cm^{-1} .

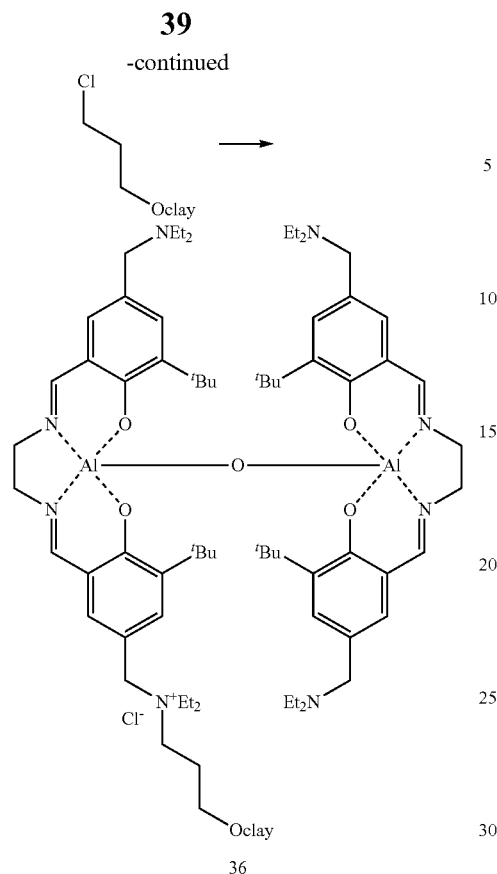
Example 8

(a) Synthesis of Modified Al Pillared Clay

(3-Chloropropyl)-triethoxysilane (0.16 mL, 2 mmol) was added to a mixture of activated Al pillared clay (2 g) in dry toluene (25 mL) and the mixture was refluxed under N_2 for 24 hours. Then, the mixture was filtered and washed with EtOAc (4×50 mL) to give a yellow powder (95%). \square_{max} 3512 and 1028 cm^{-1} .

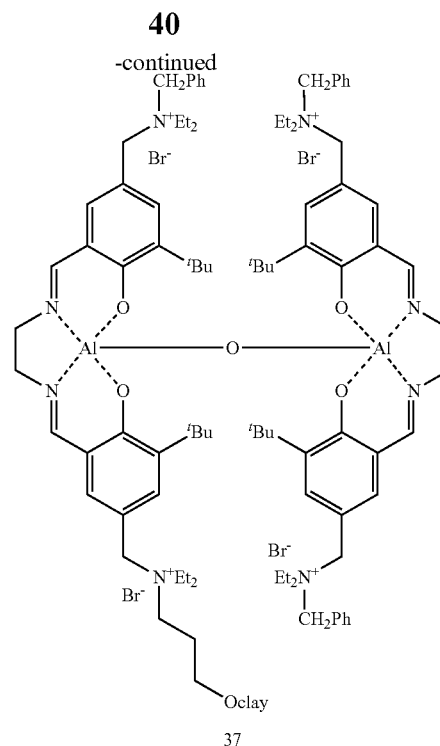
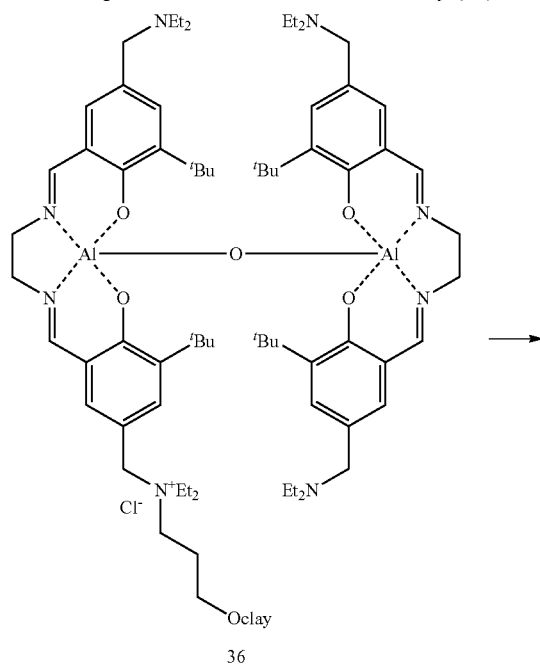
(b) Synthesis of $[\text{Al}(\text{salen})]_2\text{O}^+\text{Cl}^-$ Supported on Modified Al Pillared Clay (36)





Modified Al pillared clay (0.1 g) was added to a solution of aluminium complex (22) (0.175 g, 0.15 mmol) in CH₃CN (40 mL) and the mixture was then refluxed overnight. Subsequently, the mixture was filtered and washed with EtOAc (4×50 mL) and dichloromethane (3×50 mL) to give clay supported complex (36) as a yellow powder. \square_{max} 3410, 1627 and 1031 cm⁻¹.

(c) Synthesis of Benzylated [Al(salen)]₂O⁺Br⁻ Supported on Modified Al Pillared Clay (37)



Benzyl bromide (0.09 mL, 0.72 mmol) and tetrabutylammonium bromide (193 mg, 6 mmol) were added to a solution of supported complex (36) (0.220 g, 1 mmol) in CH₃CN (40 mL) and the resulting mixture was refluxed overnight. Subsequently, the mixture was filtered and washed with EtOAc (4×50 mL) to give clay supported complex (37) as a yellow powder. \square_{max} 3415, 1627 and 1028 cm⁻¹.

Example 9

Synthesis of Styrene Carbonate Using Supported Catalysts (35) and (37)

Styrene oxide (0.2 g, 1.66 mmol) and catalyst (35) or (37) (0.083 g, 0.5 mmol/g support) were placed in a sample vial fitted with a magnetic stirrer bar and placed in a large conical flask. The conical flask was placed in an oil bath thermostatted at 26° C. Cardice pellets were added to the conical flask which was fitted with a rubber stopper pierced by a deflated balloon. The contents of the reaction vial were stirred for 24 hours during which time the balloon inflated as the cardice pellets evaporated. The reaction was filtered to remove supported catalyst and the solution analysed by GC to determine the conversion of styrene oxide into styrene carbonate.

Catalyst	Conversion (%)
35	86
37	21

Example 10

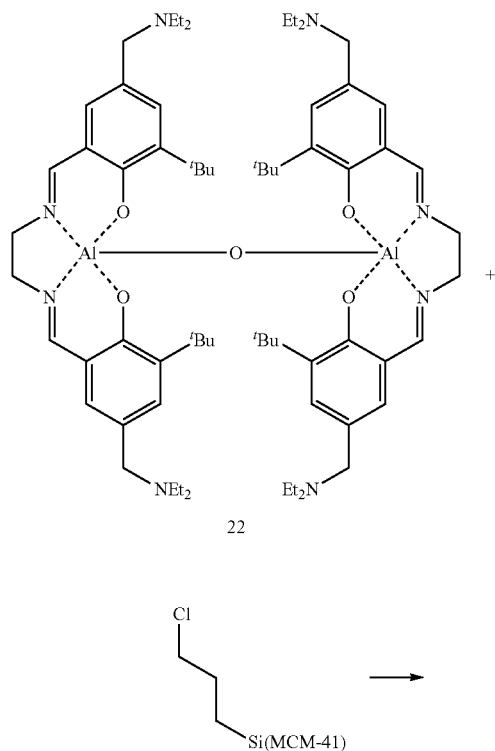
(a) Synthesis of Modified MCM-41

(3-Chloropropyl)-triethoxysilane (0.16 mL, 2 mmol), was added to a suspension of activated MCM-41 (2 g) in dry toluene (25 mL) and the mixture refluxed under N₂ for 24

41

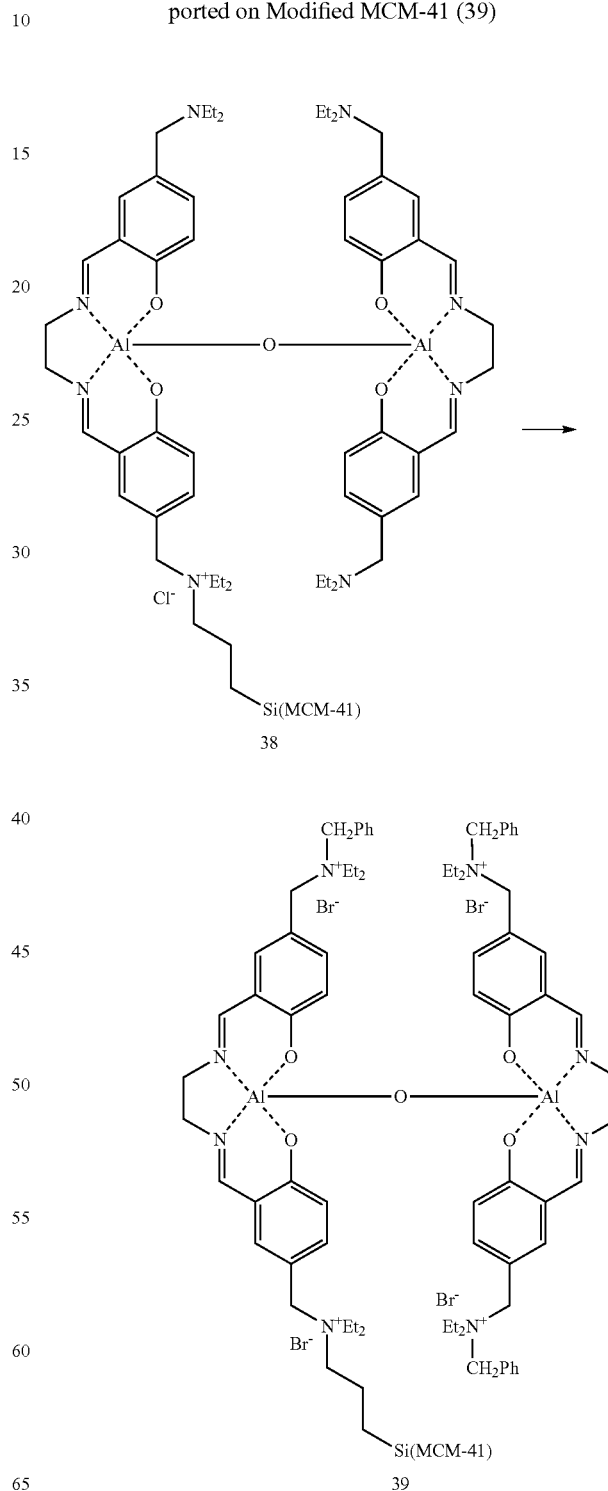
hours. The mixture was then filtered and washed with EtOAc (4×50 mL) to give a white powder (94%). \square_{\max} 2681, 1711, 1057 and 807 cm^{-1} .

(b) Synthesis of $[\text{Al}(\text{salen})]_2\text{O}^+\text{Cl}^-$ Supported on Modified MCM-41 (38)

**42**

3-Chloropropyl modified MCM-41 (0.52 g) was added to a solution of aluminium complex (22) (1.50 g, 0.45 mmol) in CH_3CN (40 mL) and the mixture refluxed overnight. Then, the reaction was filtered and washed with EtOAc (6×50 mL) to leave MCM-41 supported complex (38) as a yellow powder (0.86 g, 86%). \square_{\max} 3122, 1628, 1057 and 789 cm^{-1} .

(c) Synthesis of Benzylated $[\text{Al}(\text{salen})]_2\text{O}^+\text{Br}^-$ Supported on Modified MCM-41 (39)



43

Tetrabutylammonium bromide (0.20 g, 0.6 mmol) and benzyl bromide (0.13 g, 1 mmol) were added to a suspension of supported aluminium complex (38) (200 mg, 0.15 mmol) in CH₃CN (30 mL) and the mixture was refluxed overnight. Then, the mixture was washed with EtOAc (4x50 mL) to leave MCM-41 supported complex (39) as a yellow powder (0.22 g, 98%). \square_{max} 3452, 1634, 1052 and 947 cm⁻¹. ICPMS (5 mg of supported catalyst digested with 5 mL of 1M HCl) gave an aluminium concentration of 22.55 ppm, corresponding to a catalyst loading of 0.47 mmol per gram of support.

Example 11

Synthesis of Styrene Carbonate Using Supported Catalyst (39)

Styrene oxide (1.66 mmol), catalyst (39) (0.0415 mmol) and propylene carbonate (0.845 g) were placed in a sample vial fitted with a magnetic stirrer bar and placed in a large conical flask. The conical flask was placed in an oil bath thermostatted at 26° C. Cardice pellets were added to the conical flask which was fitted with a rubber stopper pierced by a deflated balloon. The reaction was stirred for 24 hours with samples being removed after 3, 6 and 24 hours for analysis by GC/MS to determine the conversion of epoxide to cyclic carbonate. The results were:

Time (hours)	Conversion (%)
3	12
6	23
24	57

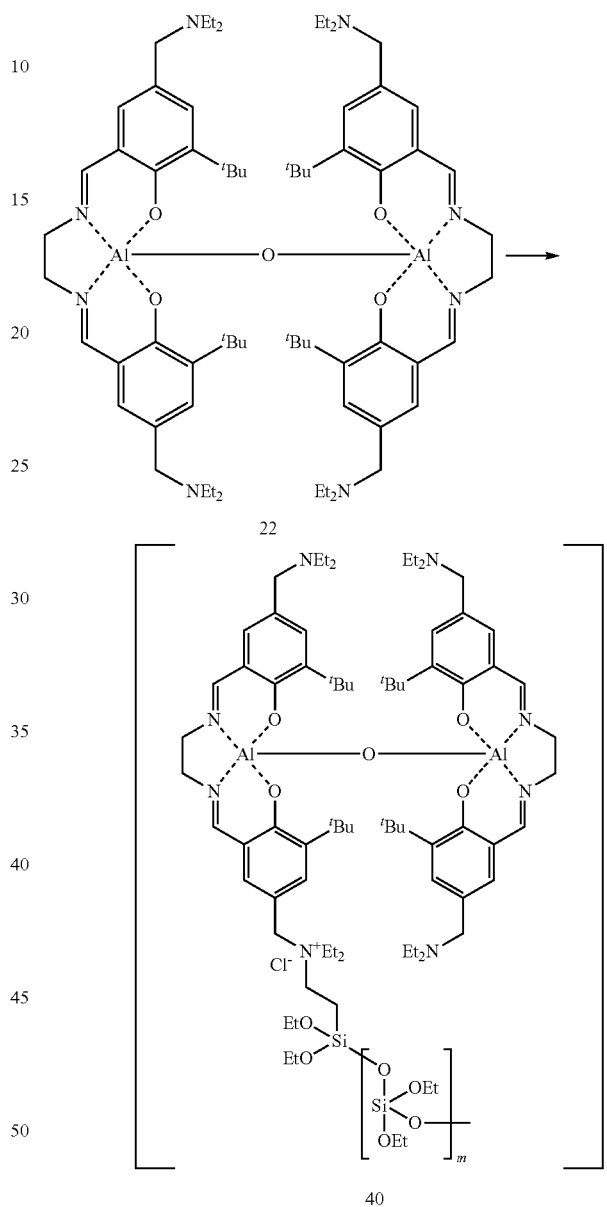
Example 12

Synthesis of Ethylene Carbonate Using Supported Catalyst (39)

Catalyst (39) (0.0503 mmol) and propylene carbonate (1.0 g) were added to a reaction vial to which pre-cooled ethylene oxide (2.01 mmol) was added. The reaction vial was fitted with a magnetic stirrer and placed inside a stainless steel reaction vessel along with sufficient cardice pellets to pressurise the system to approximately 6 atmospheres. The stainless steel reactor was sealed and the reaction left to stir for 24 hours after which the reaction mixture was taken up in ethyl acetate and filtered to remove the catalyst. The ethyl acetate was evaporated under reduced pressure and the weight of the residue determined. The relative composition of propylene and ethylene carbonates was determined by GC/MS and used to calculate that a 93% conversion of ethylene oxide to ethylene carbonate had been achieved.

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Example 13

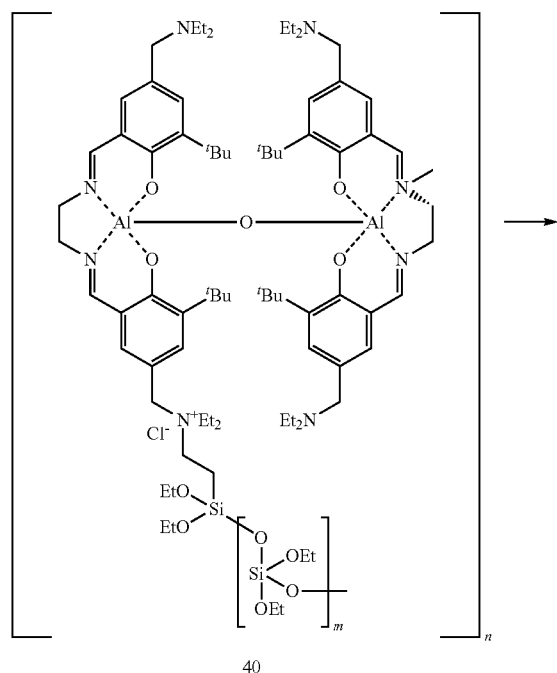
(a) Synthesis of [Al(salen)]₂O⁺Cl⁻ Supported on solgel (40)

m is approximately 10

(3-Chloropropyl)-triethoxysilane (0.12 g, 0.5 mmol) was added to a solution of aluminium complex (22) (0.55 g, 0.5 mmol) in CH₃CN (40 mL) and the reaction was refluxed overnight. Then the solvent was removed to leave a product which was dissolved in EtOH (2 mL). Si(OEt)₄ (1.12 mL, 5 mmol) was added to this solution and the mixture stirred for 2 minutes at room temperature. Then, H₂O (3 mL) and NH₄OH (3 drops) were added and the mixture was vigorously stirred for 5 min. The mixture was left undisturbed for 5 days and then placed in an oven at 110° C. for further two days. The resulting solid was washed with isopropanol (2x25 mL) and

45

CH_3CN (2×25 mL) and dried overnight at 110° C. to leave the solgel supported catalyst (40) (0.42 g, 41%). \square_{max} 2914, 1633 and 1067 cm^{-1} .



m is approximately 10

(b) Synthesis of Benzylated $[\text{Al}(\text{salen})]_2\text{O}^+\text{Br}^-$ Supported on solgel (41)

Tetrabutylammonium bromide (0.20 g, 0.6 mmol) and benzylbromide (0.13 g, 1 mmol) were added to a suspension of supported aluminium complex (40) in CH_3CN (30 mL) and the mixture refluxed overnight. Then, the mixture was washed

46

with EtOAc (4×50 mL) to leave solgel supported catalyst (41) as a yellow powder (0.52 g, 96%). \square_{max} 3562, 1629 and 1052 cm^{-1} . ICPMS (5 mg of supported catalyst digested with 10 mL of 1M HCl) gave an aluminium concentration of 13.65 ppm, corresponding to a catalyst loading of 0.51 mmol per gram of support.

Example 14

Synthesis of Styrene Carbonate Using Supported Catalyst (41)

Styrene oxide (1.66 mmol), catalyst (41) (0.0415 mmol) and propylene carbonate (0.845 g) were placed in a sample vial fitted with a magnetic stirrer bar and placed in a large conical flask. The conical flask was placed in an oil bath thermostatted at 26° C. Cardice pellets were added to the conical flask which was fitted with a rubber stopper pierced by a deflated balloon. The reaction was stirred for 24 hours with samples being removed after 3, 6 and 24 hours for analysis by GC/MS spectroscopy to determine the conversion of epoxide to cyclic carbonate. The results were:

Time (hours)	Conversion (%)
3	10
6	20
24	52

Example 15

Synthesis of Ethylene Carbonate Using Supported Catalysts (29), (35) and (41)

(a) Catalyst (41) (0.0503 mmol) and propylene carbonate (1.0 g) were added to a reaction vial to which pre-cooled ethylene oxide (2.01 mmol) was added. The reaction vial was fitted with a magnetic stirrer and placed inside a stainless steel reaction vessel along with sufficient cardice pellets to pressurise the system to approximately 6 atmospheres. The stainless steel reactor was sealed and the reaction left to stir for 24 hours after which the reaction mixture was taken up in ethyl acetate and filtered to remove the catalyst. The ethyl acetate was evaporated in vacuo and the weight of the residue determined. The relative composition of propylene and ethylene carbonates was determined by GC/MS and used to calculate that a 97% conversion of ethylene oxide to ethylene carbonate had been achieved.

(b) The above procedure was used but with catalyst (29) and resulted in 95% conversion of ethylene oxide to ethylene carbonate after a reaction time of 24 hours.

(c) The above procedure was used but with catalyst (35) and resulted in 81% conversion of ethylene oxide to ethylene carbonate after a reaction time of 24 hours.

Example 16

Use of Immobilised Catalysts to Convert Ethylene Oxide into Ethylene Carbonate Under Continuous Flow Conditions

The flow reactor is illustrated in FIG. 1. Ethylene oxide was collected from a commercially supplied cylinder as a liquid in a cooled beaker at -78° C. and placed, with a magnetic stirrer bar, inside a 360 mL pre-cooled (-10 to -40° C.) stainless

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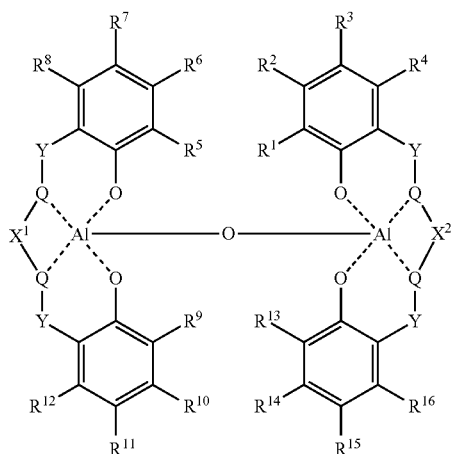
steel pressure vessel (3). The vessel was then sealed. Nitrogen and carbon dioxide gases were supplied from cylinders via mass flow controller units (1) and their respective lines merged to the inlet of the pressure vessel (see diagram). All tubing used in the system was composed of stainless steel with an internal diameter of approximately 1.6 mm. The temperature of the pressure vessel (3) was controlled by a cryostatically cooled bath (2) to provide the required rate of evaporation of ethylene oxide at a particular flow rate of N₂ and CO₂. This was determined by passing the vessel outlet line directly into a GC system (6) fitted with a column capable of separating the three gases. The vessel outlet line was then connected to a stainless steel tubular reactor (4) (15 cm×10 mm) packed with a solid supported catalyst and plugged at both ends with a small volume of cotton. The tubular reactor (4) was either kept at ambient temperature or immersed in a thermostatted water bath. The mixture of CO₂, ethylene oxide and N₂ was passed through the reactor column at a steady flow rate. The outlet of the reactor (4) was connected to a sealed glass vial (5) via a needle to collect any non-gaseous products. The outlet from the product receptacle passed to a GC system (6) which was used to determine the concentrations of CO₂, N₂ and ethylene oxide in the effluent gas stream. The results obtained with both silica and polystyrene supported catalysts are given in the following table.

Run	Catalyst (amount g)	N ₂ flow (mL/min)	CO ₂ flow (mL/min)	Pressure vessel temperature (° C.)	Ethylene oxide consumption (mL/h)	Time (h)	Reactor temperature (° C.)	Ethylene carbonate yield
1	29 (2.51)	25	25	-40	1.0	19	ambient	0.14 g, 0.15%
2	35 (1.95)	25	25	-40	1.0	19	ambient	0.08 g, 0.1%
3	35 (1.17)	2.5	2.5	-10	0.21	120	ambient	1.1 g, 1.5%
4	35 (1.17)	2.5	1.0	-10	0.15	96	ambient	1.5 g, 4%
5	35 (3.52)	2.5	1.0	-10	0.15	46	ambient	2.4 g, 21%
6	35 (3.52)	2.5	1.0	-10	0.15	25	50	3.4 g, 53%
7	35 (3.52)	2.5	1.0	-10	0.15	7	60	1.49 g, 80%

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What is claimed:

1. A process for the production of cyclic carbonates comprising contacting an epoxide with carbon dioxide in the presence of a dimeric aluminium(salen) catalyst of formula I:



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48

wherein:

Y-Q is CR^{C1}=N, where R^{C1} is selected from H and optionally substituted C₁₋₄ alkyl;

each of the substituents R¹, R², R³, R⁵, R⁶, R⁷, R⁹, R¹⁰, R¹¹, R¹³, R¹⁴, and R¹⁵, is independently selected from H, optionally substituted C₁₋₇ alkyl, L-A and L-A';

R⁴=R⁸=R¹²=R¹⁶=H;

L is a single bond or an unsubstituted C₁₋₃ alkylene group;

A is an ammonium group paired with a counterion selected from Cl, Br and I;

A' is an ammonium linking group bound to a solid support and paired with a counterion selected from Cl, Br and I;

X¹ and X² are independently

(i) a C₂₋₅ alkylene chain; or

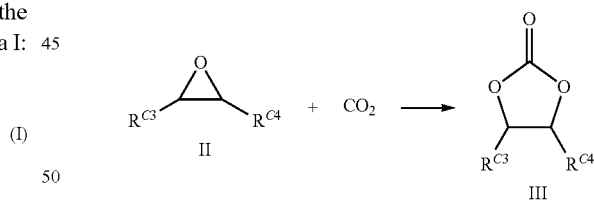
(ii) a divalent group selected from C₅₋₇ cyclic alkylene;

provided that:

at least one of R¹, R², R³, R⁵, R⁶, R⁷, R⁹, R¹⁰, R¹¹, R¹³, R¹⁴, and R¹⁵ is L-A'.

2. The process according to claim 1, carried out at a temperature of between 0 and 140° C. and/or a pressure of between 0.5 and 5 atm.

3. The process of claim 1, wherein the catalysed reaction is:



wherein R^{C3} and R^{C4} are independently selected from H, optionally substituted C₁₋₁₀ alkyl, optionally substituted C₃₋₂₀ heterocyclyl and optionally substituted C₅₋₂₀ aryl, or R^{C3} and R^{C4} form an optionally substituted linking group between the two carbon atoms to which they are respectively attached.

4. The process according to claim 3, wherein R^{C4} is H.

5. The process according to claim 3, wherein R^{C3} is selected from optionally substituted C₁₋₄ alkyl and optionally substituted C₅₋₇ aryl.

6. The process according to claim 1, carried out in a flow reactor or a gas flow reactor.

7. The process according to claim 1, carried out under continuous flow conditions.

8. The process according to claim 1, carried out under solvent-free conditions or using propylene carbonate as a solvent, and/or wherein one of $R^1, R^2, R^3, R^5, R^6, R^7, R^9, R^{10}, R^{11}, R^{13}, R^{14}$, and R^{15} is selected from L-A' and A' is selected from $-\text{NH}(\text{CH}_3)(\text{CH}_2)-$, $-\text{NH}(\text{CH}(\text{CH}_3)_2)(\text{C}(\text{CH}_3)_2)-$,
 $-\text{N}(\text{CH}_3)_2(\text{CH}_2)-$, $-\text{N}(\text{CH}_2\text{CH}_3)_2(\text{CH}_2\text{CH}_2)-$,
 $-\text{N}(\text{CH}_2\text{CH}_3)_2\text{CH}_2-$, $-\text{N}(\text{CH}_2\text{CH}_3)_2(\text{CH}_2\text{CH}_2\text{CH}_2)-$,
 and $-\text{NHPh}(\text{CH}_2)-$. 5

9. The process according to claim 1, wherein L is an unsubstituted C_{1-3} alkylene group. 10

10. The process according to claim 1, wherein X^1 and X^2 are independently selected from $-(\text{CH}_2)_n-$ and n is 2 or 3

or

wherein X^1 and X^2 independently represent C_6 cyclic alkylene 15

or

wherein X^1 and X^2 independently represent a divalent group selected from C_{5-7} cyclic alkylene and is unsubstituted

or

wherein X^1 and X^2 are both $-\text{C}_2\text{H}_4-$. 20

11. The process according to claim 1, wherein the ammonium counter group is Br^- .

12. The process according to claim 1, wherein the ammonium group A is chosen from $-\text{N}(\text{CH}_2\text{CH}_3)_3$ and $-\text{N}(\text{CH}_2\text{CH}_3)_2(\text{CH}_2\text{Ph})$ or wherein the solid support is optionally a silica support. 25

13. The process according to claim 1, wherein $X^1=X^2=\text{C}_2$ alkylene or C_6 cyclic alkylene.

14. The process according to claim 1, wherein C_{1-7} alkyl is butyl. 30

15. The process according to claim 1, wherein $\text{R}^{\text{C}1}$ is H.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,273,024 B2
APPLICATION NO. : 13/887787
DATED : March 1, 2016
INVENTOR(S) : Michael North

Page 1 of 2

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:


In the Specification

Column 21, In line 12, after “step.” no new paragraph

Column 21, In line 21, after “.4795” replace “.” with --,--

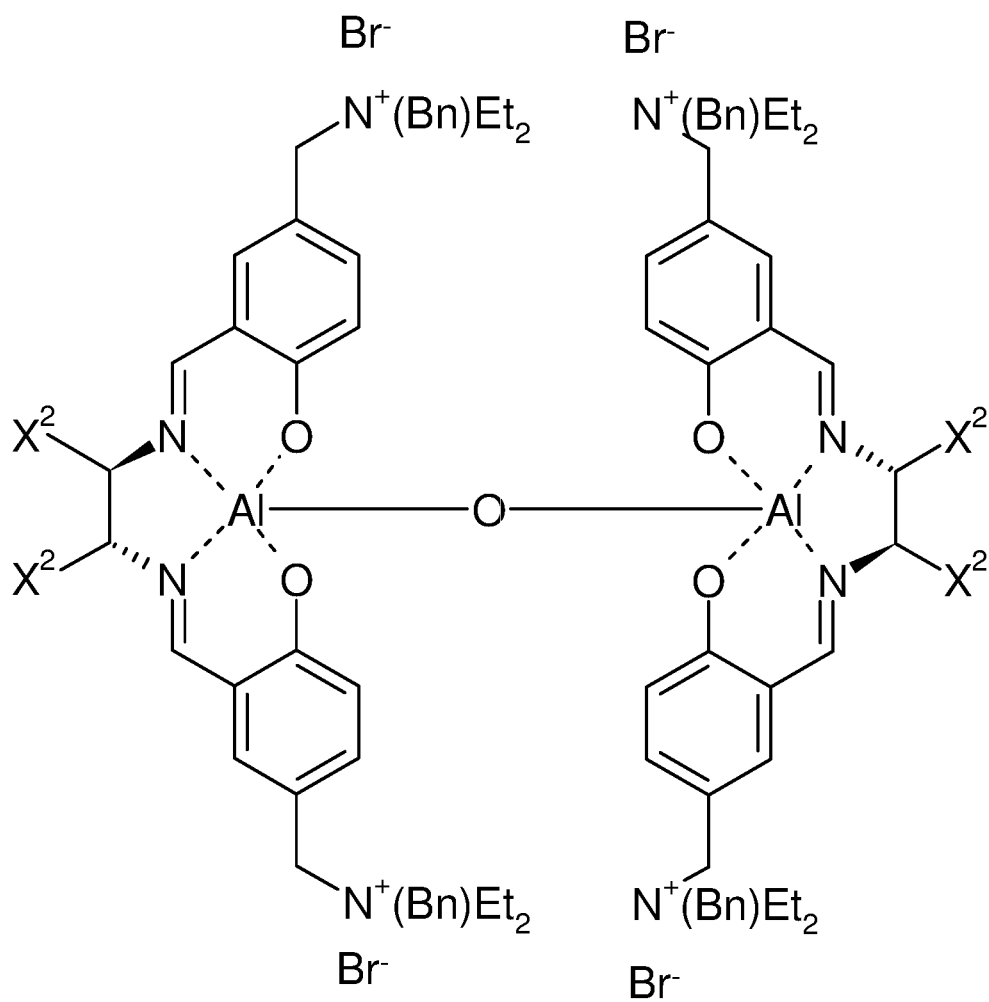
Column 22, In line 65, after “(30).” no new paragraph

Signed and Sealed this
Second Day of August, 2016

A handwritten signature in black ink, reading "Michelle K. Lee". The signature is fluid and cursive, with the first letters of each name being capitalized and prominent.

Michelle K. Lee
Director of the United States Patent and Trademark Office

Column 29, lines 32 to 54, should read:



25: $\text{X}^2 = (\text{CH}_2)_4$

26: $\text{X}^2 = \text{H}$